

# ANNALS OF INTERNAL MEDICINE

PUBLISHED MONTHLY BY

The American College of Physicians

VOL. 37 (O.S., VOL. XLII)

NOVEMBER, 1952

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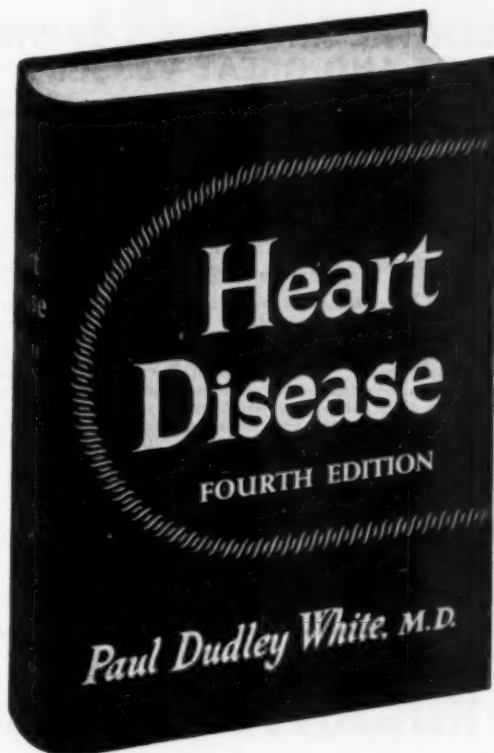
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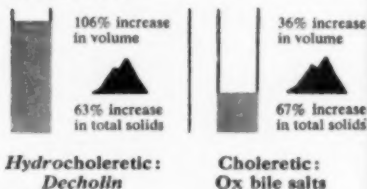
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Tested in MORE THAN 100 clinics...  
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Brand of specially prepared and highly purified  
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... a "chemical fence" for the alcoholic  
Supplied in tablets of 0.5 Gm.,  
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August 2 1952  
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3. Antispasmodic

Now you can add the  
"MISSING FOURTH"  
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4. ANTILYSOZYME

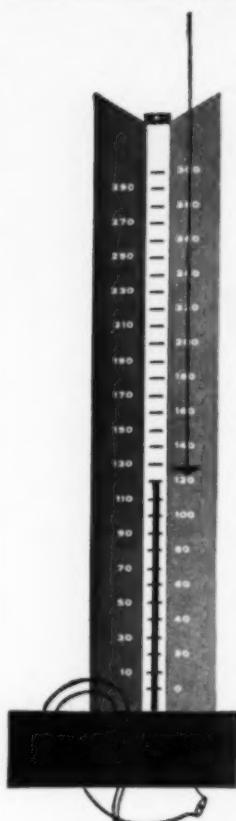
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DOSAGE: 2 Kolantyl tablets or 2 to 4 teaspoonfuls of Kolantyl Gel every 3 hours as needed for relief.  
1. Hufferd, A. R., *Rev. of Gastroenterology*, 18:588, 1951  
2. Miller, B. H., *J. So. Carolina M. A.*, 48:1, 1952  
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1. Lindsay, A. E., Goswami, W. H., and Chapman, J. S.: *Dis. Chest*, 20:533, Nov., 1951.
2. Conant, N. J., Jr.: *Am. Jour. Med.*, 6:309, Mar., 1949.
3. Emmert, J.: *J.A.M.A.*, 141:22, Sept. 3, 1949.

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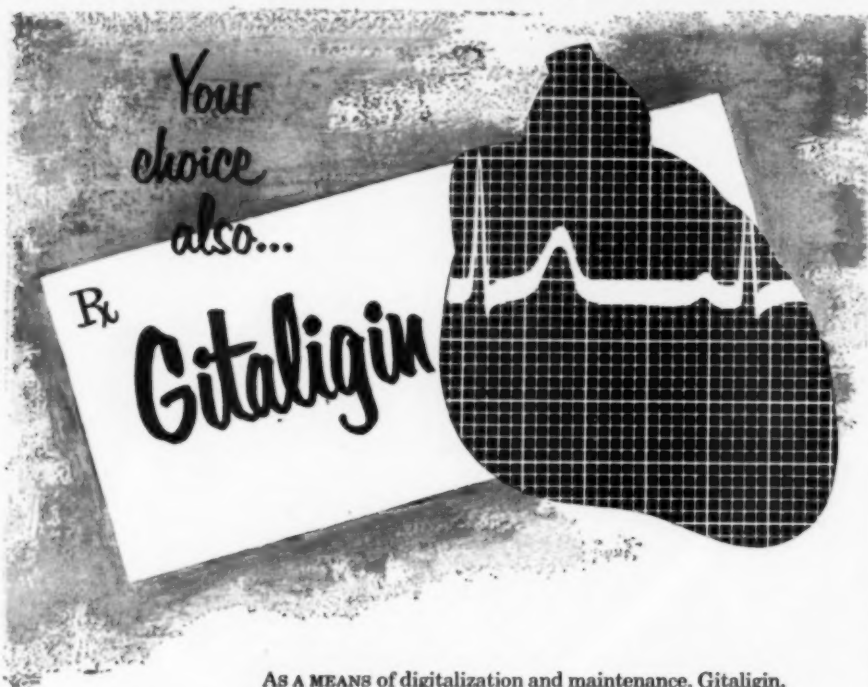
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\*Kramer, P. and Engelke, K. J., *Med. Clin. North Amer.* 32: 1227, 1948

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**GITALIGIN** supplied in 0.5 mg. tablets, scored. Bottles of 30 and 100. White Laboratories, Inc., Kenilworth, N. J.

1. Batterman, R. C.; DeGraff, A. C.; Gutner, L. B.; Rose, O. A., and Howes, J.: Studies with Gitalin (amorphous) for the Treatment of Patients with Congestive Heart Failure, *Am. Heart J.* **42**:292-307 (Aug.) 1951.

2. Batterman, R. C.; DeGraff, A. C., and Rose, O. A.: The Therapeutic Range of Gitalin (amorphous) Compared with other Digitalis Preparations, *Circulation* **5**:201-207 (Feb.) 1952.

3. Nalefski, L.: Personal Communication.

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with Methyltestosterone

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1. Schonf, R. S., Huret, J. W., and Williams, C.: *Med. Clin. North America (Mass. Gen. Hosp. No.)* p. 1958 (Sept.) 1949

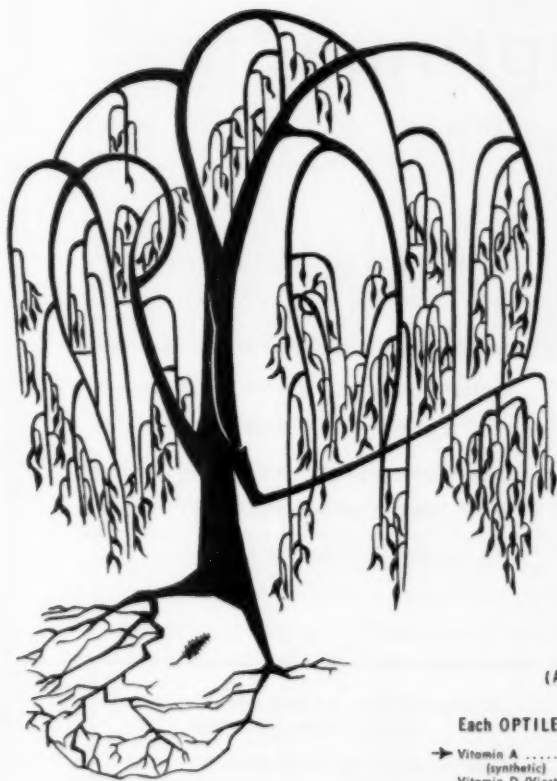


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with B<sub>12</sub> and no fish oil



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Riboflavin	5 mg.
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Ascorbic Acid	150 mg.



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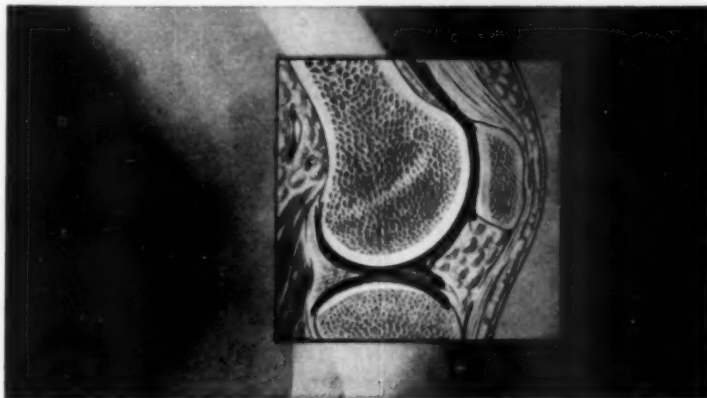
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in  
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ORAL diuretics are SIMPLER

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*with ascorbic acid*

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To secure the greatest efficacy and all the advantages of Tablets MERCUHYDRIN with Ascorbic Acid, a three-week initial supply should be prescribed . . . 25 to 50 tablets.

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NEBULIZATION of Tryptar by standard aerosol technique marks a NEW ADVANCE in the management of respiratory disorders associated with hypersecretion and accumulation of fibrinomucinous material.

(Limber, C. R.; Reiser, H. G.; Reettig, L. C., and Curtis, G. M.: Enzymatic Lysis of Respiratory Secretions by Aerosol Trypsin, J.A.M.A. 149: 816-821, (June 28) 1952.

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**in Bronchial Asthma  
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The powerful digestant action of Tryptar upon fibrin and respiratory tract mucin rapidly liquefies heavy, thick, tenacious bronchial secretions and flushes the respiratory pathways. Previously abundant expectoration dramatically decreases, putrid sputum changes its obnoxious character, and there is greater ease in breathing. Sleep, appetite, weight and well-being improve rapidly and the patient may be symptom-free for prolonged periods.

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Tryptar Aerosol is supplied in a package containing: 125,000 Armour Units (125 mg. of tryptic activity) of highly purified crystalline trypsin per vial, plus an ampule containing 3 cc. of Tryptar Diluent.



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*for your low-sodium-diet patient*

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*to help him stay on his diet*

DIASAL is an outstanding salt substitute. In addition to its fine salt taste, it contains glutamic acid to bring out the natural flavor of each food—and it can be used in cooking. At the same time its high potassium content protects your patient against potassium depletion, a hazard of low-sodium diets.<sup>1</sup>

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DIASAL—in 2-oz. shakers and 8-oz. bottles at all pharmacies.

Samples, literature and pads of low-sodium diets available on request.

1. Fremont, R. E.; Rimmerman, A. B., and Shafel, N. E.: *Postgrad. Med.* 10:216, 1951.
2. Rimmerman, A. B., et al: *Am. Pract. & Digest Treat.* 2:169, 1951.

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*Bellaspro brings prompt and effective relief from the common aches and -algias . . . turning what might have been a wasted, pain-ridden day into one of comfort and accomplishment.*

*For relief of headaches, dysmenorrhea, neuralgia, myalgia, sciatica, lumbago:*

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Equivalent in alkaloid content to 3.5 minims Belladonna Tincture	
Caffeine	½ gr.
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No. 1 with ¼ gr. codeine phosphate  
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*Rationally formulated for rapid relief of pain*

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**Unexcelled antihistamine...**

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Indicated in all allergies responding to antihistamine therapy. CHLOR-TRIMETON® maleate (chlorphenpyridamine maleate), is available in tablets, in syrup, and in solution for injection.



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for  
gastritis



mucosa of gastritis

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Suspension Maalox-Rorer is a colloidal suspension of the hydroxides of Magnesium and Aluminum.

It is pleasant to taste.

Continuous clinical use

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it causes a *quick satisfactory relief* of pain and

discomfort caused by gastritis.

The dose is two to four fluidrachms.

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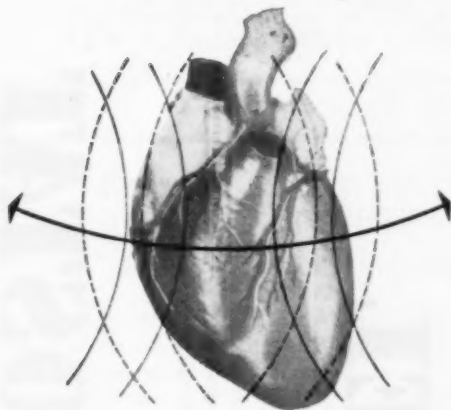


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*In cardiac decompensation*



when  
maintenance  
dosage  
is  
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Initial compensation of the failing heart may now be accomplished in hours rather than days — but maintenance of the compensated state is often a regimen of years. Continuous adjustment of the daily cardiotonic dose, which may contribute to patient morbidity, is often obviated when a preparation of reliable, constant and unvarying potency is employed.

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DIGITALINE NATIVELLE is available, at all druggists, in three strengths for precise dosage — 0.1 mg. (Pink), 0.15 mg. (Blue), 0.2 mg. (White). Because of the high order of purity, most patients are adequately maintained on 0.1 mg. daily. The average dose for digitalization is 1.2 mg. in three equal doses at 4-hour intervals.

Send for brochure: "Modern Digitalis Therapy." Clinical sample available on request.

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SUCCINYLSULFATHIAZOLE

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Sharp & Dohme

1. J.A.M.A., 127:330, 1945. 2. J.A.M.A., 128:9, 1945.

# **BACTERIOSTAT**

# ANNALS OF INTERNAL MEDICINE

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VOLUME 37

NOVEMBER, 1952

NUMBER 5

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## PRESENT STATUS OF THE BALLISTO- CARDIOGRAM\*

By ISAAC STARR, M.D., *Philadelphia, Pennsylvania*

THE President of The American College of Physicians requested me to speak at the annual meeting and then to report in this journal on the present status of the ballistocardiogram, and so this presentation will take the form of a critical essay rather than of the usual review article. I shall aim not only to summarize the more interesting features of a field which is rapidly growing in many directions, but also to view this field against the background of the changing medical interests and conceptions characteristic of our times. As no record is better than the instruments which produce it, let us start with a discussion of these.

### INSTRUMENTS

Any bright boy with a knowledge of how to work in a machine shop and put together a radio could build himself a ballistocardiograph of the type I use at small expense if he had available a moving film camera such as is found in standard electrocardiographs. But I presume that few doctors will have either the desire or the opportunity to construct such a machine for themselves, so I shall start my discussion with an account of the three types of instruments that can be purchased.

#### *Moving Table Types:*

##### A. High frequency instruments.

Instruments<sup>1, 2, 3, 12, 42</sup> of the type I prefer consist of a suspended table on which the subject lies. The table can be moved freely in the long axis

\*An amplified version of a presentation delivered at the Thirty-third Annual Session of the American College of Physicians, Cleveland, Ohio, April 21, 1952.

From the Department of Therapeutic Research, University of Pennsylvania, Philadelphia.

Much of my own work mentioned herein was supported by a research grant from the National Heart Institute of the National Institutes of Health, Public Health Service.

of the subject's body but is prevented from moving laterally, and movement in the longitudinal direction is opposed by a very strong spring, so that it is at a minimum. The minute motion which does take place, after high magnification by an optical or an electrical system, is photographed on a moving film camera or recorded by an ink writer. No damping is added, the large amount of damping present in the body of the subject being adequate. In these instruments the natural frequency of the mechanism is above the frequencies which we desire to record in the ballistocardiogram.

B. Low frequency instruments.

In the ballistocardiographs designed by Dr. Nickerson<sup>3,4</sup> of New York and now in use in several clinics,<sup>5</sup> the longitudinal movement of the table is not strongly opposed and mechanical damping must be added. In these instruments the natural frequency is below that to be recorded.

The contour of the normal records obtained by Dr. Nickerson's low frequency machine bears a strong resemblance to those secured by the high frequency instruments but the two records are not identical, the systolic waves of his records being of longer duration than those of mine; indeed, on inspection they look like integrals of my records, as I would expect from theoretic considerations.

Those using apparatus of the low frequency type have the right to claim certain theoretic advantages over my apparatus, while the many who use the high frequency type are more impressed by the fact that this set-up has not only certain theoretic advantages itself,<sup>6,12</sup> but also an important practical advantage, for with the low frequency ballistocardiograph one finds it difficult or impossible to secure records of cardiac impacts unless the subject holds his breath, and just how the subject holds his breath makes a difference in the size and, in abnormal cases, of the form of the record. This seems a serious drawback for much clinical work, which is so often conducted on untrained persons who, despite some instruction, are likely to respond to the command to hold the breath in a great variety of ways which may change the ballistic record, and so create difficulty in securing agreement of duplicate estimations on the same subject, and increase the scatter when normal standards are sought.

Also in using this method<sup>4,5</sup> the damping is adjusted to the critical level while dead weights such as sandbags, made equal to the subject's weight, are on the table; then these weights are removed, the subject lies on the table and, after a suitable interval, the record is taken. But the body itself is heavily damped, and this damping, added to that inserted in the absence of the body, would result, in my opinion, in an overdamped system. This might have certain advantages, but it would surely interfere with the production of a true record of the rapid changes in the cardiac forces.

The truth is that neither method is as yet theoretically perfect, and it is sobering for all ballistocardiographers to remember that we can never hope to record with absolute accuracy forces generated in the center of the body by apparatus placed outside it, because the body tissues are not a perfect

medium for the transmission of the forces. So, as with many methods in medicine, we must be content to proceed without having attained theoretic perfection, and I have continued to use ballistocardiographs of the high frequency type because they have proved to be reliable, inexpensive to operate and maintain, to give very reproducible results,<sup>7,8</sup> and to be extremely easy to use. This form is the simplest to operate; for it is permanently set up and does not have to be adjusted for each subject. But, in any event, both low and high frequency instruments provide perfectly proper approaches to the problem of detecting abnormalities of cardiac function.

A static calibration for sensitivity can be readily applied to all apparatus of the moving table type. By applying a known force to the table, such as a weight suspended over a pulley, the base line of the record is deflected a measurable distance. Such a simple calibration, though not ideal for a system in which resonance may be a factor, makes quantitative work possible. In our original ballistocardiograph, the effect of resonance on the wave areas was minor.<sup>1</sup>

*Portable or Direct Body Types:* Different from these two moving table types is the family of portable ballistocardiographs<sup>9</sup> which derive their inspiration from Dr. Dock of New York. In these the subject lies supine on a nonmoving surface, such as the floor, or on a rigid table (the hope that reliable records could be secured from a patient in bed has been abandoned), and the movement between the body and the nonmoving surface is recorded, usually from a bar across the shins. Dr. Dock has solved with great ingenuity the electrical engineering problem of adapting standard electrocardiographic equipment to recording this record. I shall not attempt to describe the great variety of pick-up units and electrical circuits that may be used in apparatus of this kind. With one of his instruments in which the pick-up unit was of the coil and magnet type, Dr. Dock and I made simultaneous records using his apparatus on a subject lying on the table of my high frequency ballistocardiograph with his heels off the foot plate, and the contour of the two records we secured was practically identical. However, I do not wish to convey the idea that such good records can readily be obtained by every doctor using any one of the multiplicity of devices now being sold for the purpose. Indeed, my belief is that a warning is in order, for small differences in the way the apparatus is set up may make considerable differences in the result obtained. Not infrequently I am consulted about records from portable instruments which bear no relation whatever to anything I have ever seen, and which leave me with the impression that the true ballistocardiogram is being overwhelmed by artefacts.

Those who work with instruments of the Dock type have been at a great disadvantage because of the lack of a satisfactory method of determining sensitivity. If a constantly acting force is applied, the record is deflected only temporarily and it immediately returns to the original base line, so the method of calibration satisfactory for moving table types cannot be employed. Also, I beg you not to be deceived by the manufacturer's sales talk,

which suggests that the record deflection caused by the introduction of one millivolt, a device so adequate and satisfactory for standardizing electrocardiograms, is adequate to standardize ballistocardiograms recording through electrocardiographic equipment. The information this gives you is not what one wants to know, and so the test is deceiving.

Dr. Dock has attempted to meet this difficulty by calibrating by means of a blow of short duration,<sup>9</sup> but my friends who have tried this method believe that it is not yet practical for clinical work. So it appears to me that, although progress has been made and I am hopeful of eventual success, the calibration problem has not yet been solved for this type of method, leaving the users of it in a difficult position because there is no easy way of telling when their apparatus is working properly and when it is not, and in danger of interpreting as changes in the patient's condition changes in the record due in reality to slight differences in the way the apparatus was set up or was performing. Certainly as quantitative scientific instruments these devices are not yet in the same league as the moving table types.

But as clinical instruments a great deal can be said for them. Dr. Dock is entirely right in his contention that his method, even though unstandardized, can properly be used to detect qualitative differences in the relation of the waves to one another, and deviations of the form and contour of the record from the normal, and this is a large and important field. Therefore, it seems to me that those using these instruments, after acquiring sufficient skill to set them up so that true records and repeatable results can be obtained, could properly expect to detect the many changes of contour found so often in the clinic, and so obtain a better knowledge of myocardial function than is possible with the methods of clinical examination now routine. Because of the small cost and easy portability, Dr. Dock has opened up an entirely new and most promising aspect of the field.

*Other Types:* Vertical ballistocardiograms,<sup>10, 11</sup> designed to give records of subjects standing or sitting, have been in use for many years, but as many of the sick cannot assume the upright position without so much tremor that the record is ruined, this form of instrument is less satisfactory for clinical work than those in which the subject lies relaxed in the horizontal position.

*Vector* ballistocardiographs are designed to record the ballistic forces in more than one dimension of the body. Braunstein's elaborate instrument<sup>12</sup> does this simultaneously. That used by Scarborough et al.<sup>13</sup> is a high frequency table type instrument provided with a turntable which permits the subject to be rotated in relation to the line in which the forces are recorded. These still are instruments for research rather than for routine clinical utility, although very interesting results are being secured. Dr. Dock can also record lateral movements of various parts of the body with his apparatus.<sup>14</sup>

By using appropriate forms of circuits, electrical engineers can provide records which bear various mathematical relations to the movement which originated them. In *velocity* ballistocardiograms<sup>15</sup> the linear displacement

of the body has been electrically converted to give a record of the body's velocity in the hope that important abnormalities of form could thereby be made more obvious. All sorts of variations on this theme are possible. All these instruments are still in the experimental stage.

*Torsion* ballistocardiographs,<sup>18</sup> for recording rotational forces, have not yet had clinical trial.

#### RELATION OF THE BALLISTOCARDIOGRAM TO CARDIAC FUNCTION THE EXPERIMENTAL APPROACH

*Relation to Cardiac Output and Cardiac Strength:* In contrast to the electrocardiogram, the amplitude of the ballistocardiogram increases after exercise,<sup>1, 17</sup> and large ballistocardiograms are usually found in all physiologic situations in which cardiac output is known to be increased. Thus, early in these investigations<sup>1</sup> it became obvious that there must be a relation between ballistic amplitude and cardiac output, and this has been carefully studied by those using instruments which can be calibrated for sensitivity.<sup>1, 18, 19</sup> While no one claims at present that this important cardiac function can be measured with high accuracy from the amplitude of ballistocardiograms,<sup>20</sup> all the published evidence points to the fact that there is indeed a relation between them in healthy persons, that rough accuracy can be secured, and that this accuracy increases when one is dealing with changes in individuals.

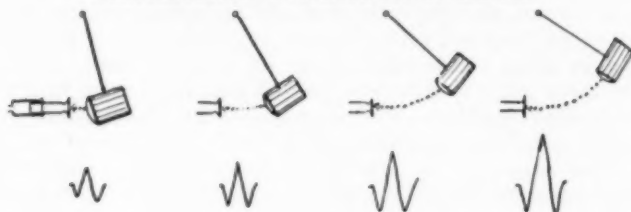
Unfortunately it was soon apparent that, in many persons with abnormal hearts, the relation between the ballistic record and the cardiac output was not the same as in the healthy.<sup>1</sup> For example, when the ballistocardiogram is abnormal in form the cardiac output is underestimated by the formula which holds for healthy subjects,<sup>1</sup> and even if the record remains normal in form the abnormal movement of blood occurring in so many cardiac diseases might throw the estimate off. Therefore, at the present state of our knowledge it seems unwise to place confidence in estimates of cardiac output from the ballistocardiogram taken in many patients with heart disease and in those in extreme shock. On the other hand, the cardiac output method popular today, the Fick with intracardiac catheterization, is very difficult, expensive and time-consuming for the operator, and for the patient amounts to a minor operative procedure done under a local anesthetic, usually after premedication with barbiturates. In most clinical conditions the danger has proved to be negligible, but there is a small but definite hazard of untoward complications, and the study of certain interesting types of disease, such as cardiac infarction, has been wisely avoided because of the probability of risk to the subjects. Also, one wonders how many untrained subjects can undergo such an elaborate procedure without an emotional reaction which would alter the very function one is trying to measure. Obviously, therefore, efforts to improve the estimation of cardiac output and cardiac strength from simple clinical measurements which contain so little to disturb the



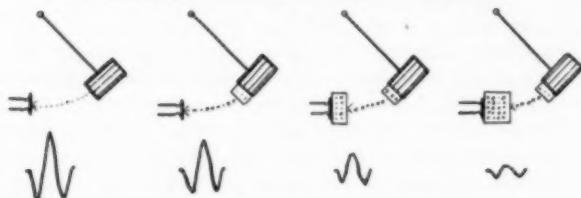
subject, and which can be repeated as often as one wishes, must be continued.

With such thoughts in mind, we have been using for several years a type of preparation which simulates cardiac function in cadavers at necropsy.<sup>21</sup> Large cannulas are tied into the aorta and pulmonary arteries and led out to two 100 c.c. syringes, the plungers of which are arranged to be driven in by a large mallet, weighing 56 pounds and heavily padded on its striking surface, which swings on an axis over five feet in length. We impose a diastolic

### BALLISTO AMPLITUDE AND CARDIAC POWER INCREASING STRENGTH OF BLOW



### SOFTENING THE BLOW BY PADDING



### THE AMPLITUDE OF THE BALLISTO IS RELATED TO FORCE PER UNIT OF TIME

FIG. 1. Diagram of the effect of increased strength of "cardiac" blow and of "hard" and "soft" blows on the ballistocardiogram, illustrating results secured in experiments on cadavers in whom cardiac function was simulated at necropsy while they lay on a ballistocardiograph.

pressure on the cadaver by allowing fluid to run into the femoral artery from a perfusion bottle elevated to give the desired diastolic level.

With all in readiness, the clamp on the tube from the perfusion bottle is opened and, when a suitable diastolic pressure level has been attained, the inflow is stopped and systole is simulated by burning through the thread holding up the padded mallet which, after falling through its arc, drives in the syringe pistons, the position of which is recorded at every instant by a light beam system. We now have over 200 of these simulated systoles in



over 20 cadavers. In most, water or saline was used as the perfusion fluid, but recently we have perfected our technic to the point of using compatible blood, with noteworthy improvement in the results.<sup>22</sup> Figure 1 shows the general type of results secured,<sup>22</sup> and illustrates very clearly the general relation between the ballistic record and cardiac function.

When the systolic force is increased by dropping the mallet through a larger and larger arc, the amplitude of the ballistocardiogram increases paripassu; hence the force of the cardiac blow is the major factor in the amplitude of the ballistocardiogram. But a different kind of experiment shows that there is another important factor, the way that force is applied. If we make a series of equal blows by dropping the mallet through the same arc, but increase the amount of rubber padding between the mallet and the syringe handle, the ballistocardiogram becomes steadily smaller in amplitude. The effect of the increased padding is to spread the blow in time, so that, while the total force delivered remains almost the same, the maximal force delivered in a single unit of time is much less. There is a close analogy here to the common experience of driving a nail with a hammer. Everyone knows the difference between the effect of a sharp and a cushioned blow, and the ballistocardiograph records this type of information about the heart's contraction.

So the more recent evidence indicates that the amplitude of the ballistocardiogram is more closely related to cardiac power than to cardiac output.<sup>21</sup> Indeed, in the initial study<sup>21</sup> the closeness of the relationship was gratifying. These studies are being continued but, because of the many difficulties inherent in performing physiologic experiments at necropsy, progress has been slow. How best to combine the blood pressure value with data obtained from the ballistocardiogram to get the most accurate estimate of cardiac power is still undecided. But substantial confirmation of the reported results has been consistently secured, and it seems evident that the amplitude of the record is primarily related to the strength of the beat. The relation to cardiac output stems from the fact that the normal heart, like a sensible organ, increases its output when it beats more strongly. But in disease the heart has a means of sparing itself,<sup>23</sup> so that a weakened heart can maintain its output either unimpaired or with a minimum of impairment. It is this change in the manner of beating that alters the relation between the ballistic amplitude and cardiac output which prevails in health, making the old formulae, which yield satisfactory estimates of cardiac output in health, seriously underestimate cardiac output when the heart is weak. It is to be hoped that the new data will permit the development of formulae applicable to a wider range of clinical conditions.

*Genesis of the Individual Waves:* Experiments of the type described, in which cardiac function is simulated at necropsy, have proved the original theory that the contour of the ballistocardiogram depends on the shape of the cardiac ejection curve, that is, on the manner in which the heart ejects its blood. Since a large number of the record forms seen in the clinic can

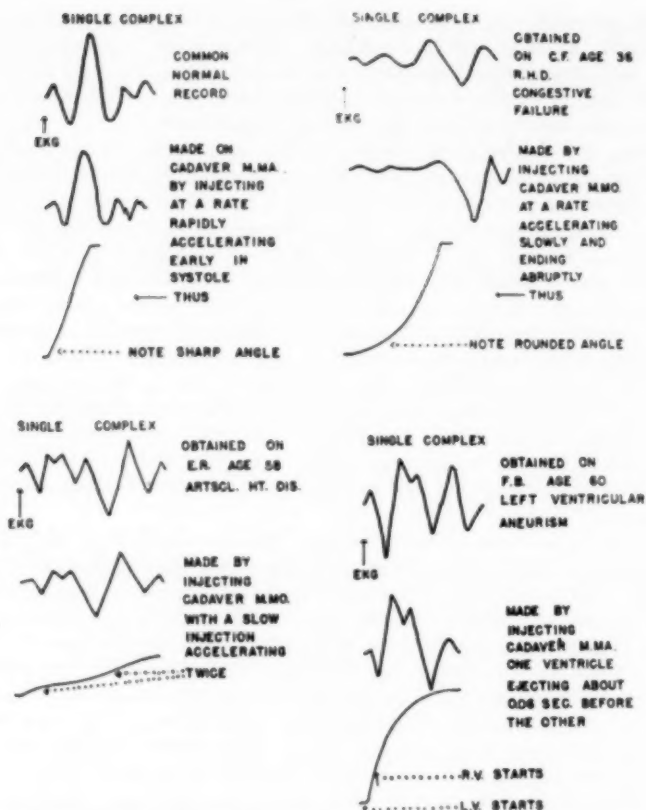


FIG. 2. Diagrams to illustrate that, by simulating cardiac function at necropsy, we can produce ballistocardiograms identical with the normal record found in healthy young adults as far as the main waves are concerned, and also closely simulate many abnormal forms found in disease. Note also the evidence that the shape of the cardiac ejection curve determines the contour of the ballistocardiogram. The drawings are careful transcriptions of the original photographic records.

The figure is divided into 4 parts. The top record of each part is a transcription of the ballistocardiogram of a single systole encountered in routine work in the clinic. Next below is a ballistocardiogram obtained by injecting the aorta and pulmonary artery of a cadaver at necropsy, selected because its contour so nearly matched that of the record above it. At the bottom is a transcription of the photographic record of the cardiac injection curve which was the genesis of the ballistocardiogram given above it in the cadaver experiment. The two lower records of each part of the figure, occurring simultaneously in the record of the cadaver experiment, are also vertically aligned for time in the reproduction.

be reproduced experimentally,<sup>21</sup> we have the right to believe that we have a firm grasp on their genesis.

Figure 2 shows that the normal ballistic contour can be reproduced by a cardiac ejection curve which accelerates rapidly initially. In the same

figure it is shown that tracings characteristic of certain abnormal hearts can be reproduced by an ejection curve which starts slowly and ends abruptly. Also, when the right and left sides eject asynchronously a notched J wave results, such as is seen in certain clinical conditions in which similar asynchronism is to be suspected. Some very complicated and bizarre records found in patients judged to have severely damaged hearts by other criteria can also be reproduced experimentally by bizarre cardiac ejection curves in our cadaver preparations. Most of the abnormalities of the I, J and K waves that we see in the clinic we now know how to reproduce experimentally.

Our experimental studies have as yet thrown no light on the genesis of the H wave or of the abnormal diastolic waves, which are not reproduced by injecting into the aorta and pulmonary artery; but often changes in the condition of patients provide data of the experimental type. The H wave is a most interesting wave; certainly, recent evidence has strengthened the view that the auricular contraction is an important factor in its genesis,<sup>24</sup> for small waves follow the isolated auricular contraction in cases of heart block,<sup>24, 26, 27</sup> the H wave is usually present when the electrocardiographic P wave is present in the normal position, and the H wave is usually absent when the P wave is displaced from its normal position in block, or is altogether absent in auricular fibrillation.<sup>26, 49</sup> But there are noteworthy exceptions to both these last statements<sup>3, 25</sup>; one is shown in the record of J. B. (figure 5), so other factors undoubtedly enter the genesis of the H wave. I think especially of factors concerned with the abnormal movement of the heart and its contained blood in the preëjection phase of cardiac contraction. I recall an unusually large H wave seen in a case of ventricular aneurysm,<sup>50</sup> and I have other records of very conspicuous H waves in cases of coronary heart disease.<sup>23</sup> In some of them it is diminution of I rather than increase of H which makes the H wave conspicuous, but in others H is undoubtedly increased. I hesitate to adopt the view that the auricles are contracting abnormally strongly in such cases, although, as we are quite without knowledge about changes in auricular strength in clinical conditions, this remains a possibility. I am more inclined to account for these large H waves by abnormal movement of blood within the heart, as into an aneurysm or into a noncontracting part of the heart when contraction of the more normal remainder begins, causing a movement which would give an impact by changing the heart's center of mass before any blood was ejected. If this is the correct explanation, one should not expect to see a large H wave in every case of cardiac aneurysm or coronary infarction, because the location of the bulge would be the determining factor in the direction of the motion which, if not in the body's longitudinal direction, would not be recorded by conventional technics. I have many records of subjects with undoubted cardiac aneurysm and with infarction later demonstrated at necropsy which do not show large H waves.

I shall not attempt to enumerate all the other possible factors in the

production of H waves, but I shall mention two more. Tricuspid incompetence would permit movement of blood from the heart back into the veins where pressure is low, at a time before the intracardiac pressure has risen high enough to drive blood into the pulmonary artery where pressure is higher. From theoretical considerations one expects that such an abnormal movement of blood would produce a small footward thrust followed by a

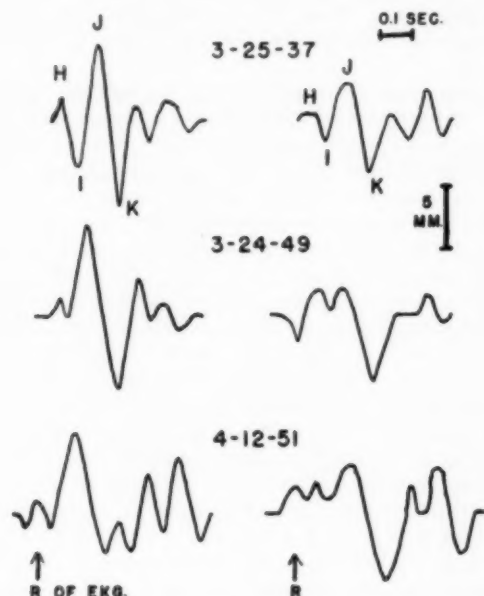


FIG. 3. Diagrams to illustrate ballistocardiograms taken on K. L. T. during the last 15 years of his life. The original records were secured by three different photographic techniques and cannot be easily compared by inspection, so scale drawings of typical large and small complexes of the respiratory cycle are given here. These permit an accurate comparison of the three records by inspection alone.

The record of March 25, 1937, was altogether normal.

That of March 24, 1949, shows great diminution of the I wave in the largest complex, which now just reaches the base line, while in the small complexes J does not exceed H and I never reaches the base line. About two thirds of the complexes of the respiratory cycle resembled the small complex shown, and only an occasional normal complex was seen anywhere in the record.

In the record of April 12, 1951, the large complexes are deceptive in appearance, and without a simultaneous electrocardiogram an error in interpretation might be made. While this large complex looks normal, the position of R (indicated by the arrow) shows that the wave just to its right is not I. This conclusion is confirmed by the use of calipers set at the cardiac cycle and so indicating the distance between the I waves seen in the smaller complexes. It can be shown by moving the calipers up the record from the complexes with an I wave to those without that the proper position for I in the large complexes is in the middle of the large upstroke. Therefore the I wave is altogether absent in the largest complexes, and H and J are fused. In the smaller complexes I appears but fails to reach the base line. No normal complexes were seen in the record.

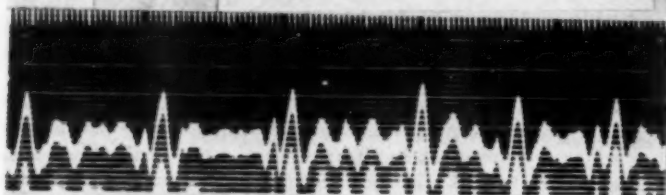
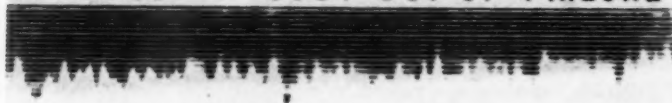
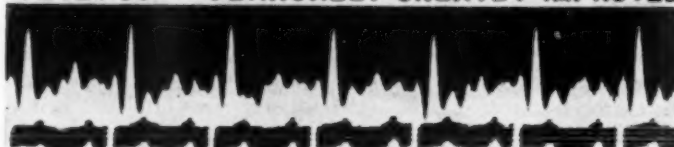
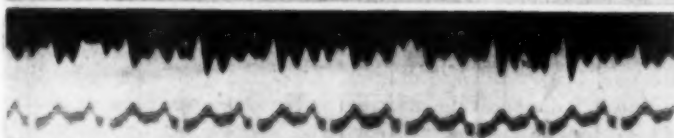
larger headward thrust in the ballistic record soon after the onset of systole. Mitral regurgitation leading back to the pulmonary veins would theoretically be less effective in producing ballistic impacts, because these veins spread laterally and in opposite directions, and so abnormal waves in them would not be recorded; but Dr. Kuo<sup>26</sup> has shown me some records well explained by this conception, as is that of J. B. in figure 4.

Also, the abnormally sudden arrest of blood entering the heart when diastole is over might initiate a wave which, traveling slowly backward into the veins, might also produce a headward thrust at the time of the H wave.

Following a clue provided by the experiment of Hamilton et al.<sup>44</sup> Brown et al.<sup>47</sup> observed that the K wave was absent in cases of coarctation of the aorta, especially during expiration, and that this abnormality disappeared after surgical restoration of the lumen. These observations marked a major advance in our knowledge of this wave. Figure 5 gives an example taken from one of my cases. Diminished K waves (usually not to the extent of those sometimes seen in coarctation) may occur in other conditions in which interference with blood flow in the aorta is a factor. In my laboratory, Dr. E. M. Hildreth has secured a record on a woman near term which showed an abnormal K wave; after delivery it returned to normal, but this does not always happen in pregnancy. In only two of my many records of drug action was the K wave affected. In one healthy medical student the K wave, normal before and after the experiment, was greatly shortened during the action of urecholine. In another student the K wave, previously short, lengthened markedly during adrenalin action. Obviously, physiologic as well as anatomic factors may be associated with the abruptness of the retardation of blood in the aorta when the systolic propelling force, which is the genesis of this wave, diminishes and stops. Changing peripheral resistance was evidently a factor in the changing K wave of these two cases.

Abnormal diastolic waves which sometimes exceed the systolic waves in height are encountered most frequently in cases with elevated venous pressure,<sup>27, 28</sup> and so are to be attributed to abnormally abrupt movement of blood as the heart is filled, creating waves which travel back into the great veins. Very large headward diastolic waves are often seen in constrictive pericarditis,<sup>9, 26</sup> disappearing after the constriction has been surgically relieved. I presume that the rush of blood into the heart in diastole, propelled by the high venous pressure, is stopped abruptly in mid-diastole, because constricted hearts suddenly reach the limit of possible expansion, the sudden stoppage causing waves to be transmitted back into the great veins where, because of the higher pressure, they would be better propagated than under normal conditions of low pressure and so would be more effective in causing abnormal diastolic ballistic waves. Such large diastolic ballistic waves are often accompanied by a third heart sound.<sup>28</sup>

I also have the record of a large diastolic wave in a case of traumatic arteriovenous communication, which disappeared after surgical closure.<sup>29</sup>

**J.B.****FEBRUARY 8, 1938****A.C. AGE 52****10/31/50****JUST OUT OF FAILURE****4/12/51****CLINICALLY GREATLY IMPROVED****S.F.****J.J.**



## THE EMPIRIC APPROACH

*General Principles in the Detection of Abnormality in Clinical Data:* Obviously the purpose of the ballistocardiogram is to permit one to distinguish health from disease, normality from abnormality. But before describing the results obtained in the clinic, certain basic principles applying to any clinical investigation of this type should be clearly understood, as they will do much to explain the course the investigation has taken and the reason for certain changes in my viewpoint as the investigation has progressed.

Doctors seem to expect that a sharp line can be drawn between normal and abnormal values for any test, and most think of diagnostic criteria in terms of limits of normality; indeed, most diagnostic tests are presented to them in this way. But because all our methods contain errors, normal limits can never be sharply defined, and the profession would have a firmer grasp on the real significance of data offered them by the methods used for the detection of disease if they thought in terms not of limits but of likelihoods. The best we can hope to do is to arrange our results in logical order, at one end of which the likelihood of normality is very great, at the other end the likelihood of abnormality is equally great, but in the middle the two shade into one another and there is no valid justification for the expectation that a sharp division between normal and abnormal can be made. Also, utility is the final criterion of how the data should best be used, and this can be determined only by prolonged study and experience. Such considerations are my answer to those who miss in my work rigid instructions for distinguishing normal from abnormal ballistocardiograms. I have been content to go along slowly and let my ideas develop with increasing experience.

One might start by relying on the clinical study now routine, and consider as normal any ballistic form found in any patient in good health whose heart is normal by the common clinical criteria. In my early publications<sup>27, 28</sup> I was much influenced by this approach, but doubts as to the wisdom of such a policy soon arose, for some of those subjects with ballistic records which, although unlike those of healthy young adults in form, had been passed as

FIG. 4. Various ballistocardiograms secured in patients. The reproduction is 7/8 actual size. The first record is taken by the old technic, the last four by the new. The moving edge of the last four records corresponds to the upper edge of the first record.

J. B. For description see text. A normal record, except for arrhythmia due to auricular fibrillation.

A. C. Age 52 in 1950. Admitted October 24, 1950, in congestive failure, with a "cooing dove" aortic diastolic murmur and cardiac enlargement. Blood pressure, 150/60 mm. of Hg. Wassermann positive. Treated with digitoxin, low salt diet and penicillin, with disappearance of the congestive failure. Diagnosis: Syphilitic aortitis. Aortic regurgitation. On April 11, 1951, patient was asymptomatic and had no evidence of congestion. Blood pressure, 170/60 mm. of Hg. She was still receiving digitoxin,  $\text{NH}_4\text{Cl}$ , and instruction about a low salt diet. She was still doing extremely well when seen on May 8, 1952. Note the striking ballistic improvement.

S. F. A 46 year old male. Blood pressure, 155/106 mm. of Hg. Diagnosed coronary heart disease. He had suffered from severe angina pectoris for six years. He was treated with radioactive iodine soon after this record was taken.

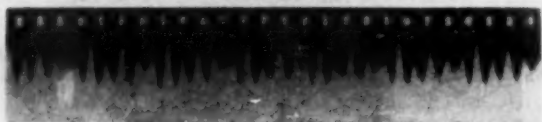
J. J. Age 58. Blood pressure, 120/40 mm. Hg. He also had severe angina and was having severe attacks of pain while in bed at night, relieved by nitroglycerin. He was diagnosed luetic heart disease with aortic regurgitation.



**F.W. AGE 39 5FT.6 130 LBS. B.P. 114/88**  
**AURICULAR FIBRILLATION**

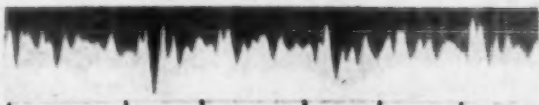
1950

10-12

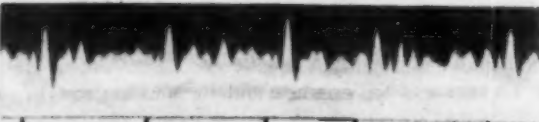


10-21 OPERATION

10-31

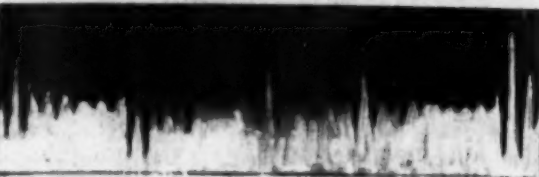


11-7



1951

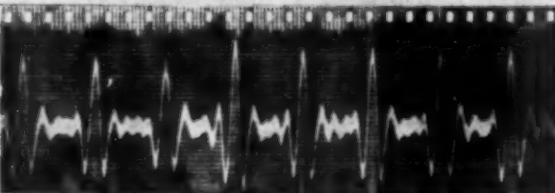
3-21



**RE**



**OPERATION**



normal, began to develop undoubted cardiac disease as the years went by. So the question arose whether a more rigid definition of the normal would not be of greater value, as it might permit one to detect myocardial abnormality earlier, or of a form different than could be detected by the more usual tests.

It seemed wise, therefore, to adopt the view that the best standard of normality of form lay in the records of healthy young adults, and this is the view now generally held.<sup>3, 52</sup> The strength of this position lies in the remarkable homogeneity of form found in the ballistocardiograms of healthy adults under 40 years of age, which makes the qualitative detection of abnormal contour a comparatively easy matter, while the more quantitative detection of abnormal amplitude can be approached by statistical methods. The chief doubt about the wisdom of this course lies in the large number of oldsters, healthy in their own estimation and normal according to the routine clinical studies, who give ballistocardiograms very different from those of healthy young adults. One asks oneself the question, "Are these people really more abnormal than their age would account for," or, better, "Is it advantageous to consider them as abnormal and so as different from those of the same age whose records have remained like those of young adults?" Evidence on this point can be sought in the after-histories of these cases: several, apparently in good health but with abnormal ballistocardiograms, when first tested, who later developed unquestioned heart disease, have already been reported<sup>17, 28, 40</sup>; in this paper I report another. This type of work must be continued and extended, as it alone will provide decisive information.

However, in passing I must comment on our lack of exact knowledge of the prognostic value of most criteria commonly used by physicians for that purpose; so little has been evaluated in terms of long after-histories. To require this for the ballistocardiogram is to insist on criteria of a type not now available for most common symptoms, signs and tests. It is doctors of the hospital or consultant type who have been writing the medical literature in recent years, and the nature of their work leads to only brief

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FIG. 5. Effect of two surgical operations on the cardiac function. Ballistocardiograms of two patients before and after operation. The reproductions are 7/8 actual size. The records in F. W. were taken by the newer technic, those on R. E. by the older. The black dots indicate the position of the electrocardiographic R wave.

F. W. Age 39. A case of constrictive pericarditis operated upon by Dr. Julian Johnson. The patient also had auricular fibrillation. Note the deterioration of the record in the immediate postoperative period, with gradual recovery and a final result which is most gratifying.

R. E. Aged 20 in 1949. A case of coarctation of the aorta. He never had symptoms, and the lesion was discovered in a routine physical examination. An excision of the coarctation with end-to-end anastomosis was performed by Dr. Julian Johnson on March 4, 1949. The orifice through the aortic constriction was a slit approximately 1 by 5 mm. when measured in the specimen.

Note the absence of K waves in the smaller complexes in the first record, secured on February 3, 1949, and their restoration in the second record, taken on February 24, 1950, as first pointed out by Brown et al.<sup>3</sup> The blood pressures taken coincidentally with the records were 180/90 and 123/80 mm. of Hg, respectively, before and after operation, and pulse returned to the vessels of the feet after operation.

contact with the patient. Long-term studies are badly needed in many fields, and here the general practitioner has a great advantage because of his prolonged contact with his patients, a fact clearly realized by Sir James MacKenzie and the reason for his move from London to the Scottish village of St. Andrew's. Let me express the hope that the family doctor will play a larger rôle in the development of important medical knowledge than has been the case in the recent past; certainly he does not lack the opportunity.

With this discussion as a background, let us now consider what has been found in ballistocardiograms taken on large numbers of healthy and sick persons, always asking ourselves how this knowledge might best be used.

*Normal Records:* Healthy young men and women give records in the normal form almost without exception. Figure 2 gives an example; in figure 3 the letters conventionally used have been placed near the waves they designate to aid readers unfamiliar with them.

Averages for normal wave size and duration have been worked out<sup>8, 28, 52</sup> and may be used as a basis for quantitative estimations of normality, but so much can be accomplished by inspection alone that most workers in the field use this method. With a little experience one recognizes the normal because the waves are present and easily identified: sharp and pointed, with a single tip. The J peak dominates the normal record. The downward directed I and K waves, smaller than J, are of approximately the same size in healthy young adults, I becoming smaller than K as age advances. The waves in diastole are much smaller than those in systole, and L is often (but not always) shorter than N in my records, but this seems not to be the case in most records taken by Dr. Dock's technic that I have seen. On the average, men give much larger wave amplitudes than women, and children give even smaller amplitudes, depending on their size.

During normal breathing the complexes in any record vary in size, normally increasing in amplitude during inspiration and decreasing during expiration.

Some quantitative normal standards for size are based on simple measurements,<sup>5, 28, 27, 52</sup> others are aimed at estimating cardiac output<sup>1, 6, 18, 27</sup>; both types are capable of distinguishing the normal from records which are abnormally too large or too small. However, as differences in instrument construction might, by causing differences in damping and resonance, affect the amplitude of response to the cardiac impacts in a way not detected by a static calibration, it would be wise for those using instruments of new design to check the values secured on a series of healthy young adults against those obtained by the older instruments before using the older data to detect abnormality.

*Abnormalities of Amplitude:* These can be detected only by the instruments that can be calibrated. Ballistocardiograms which are abnormally large are found in aortic regurgitation,<sup>27</sup> hyperthyroidism,<sup>29</sup> arteriovenous communications,<sup>29</sup> in some cases of anemia,<sup>29</sup> in the early stages of fever,<sup>29</sup> in many cases of neurocirculatory asthenia,<sup>29, 31</sup> and in emotional states such

as excitement. The amplitude increases after drugs<sup>10, 27</sup> and intravenous injections which stimulate the circulation,<sup>32, 33, 34</sup> and during anoxemia.<sup>35</sup> An increase in ballistic amplitude also occurs physiologically after food<sup>7, 33</sup> and exercise.<sup>17</sup>

Abnormally small records are found in myxedema and certain other endocrine states,<sup>36</sup> after certain drugs such as noradrenalin,<sup>27</sup> in many cases of hypertension,<sup>38</sup> and in many types of heart disease.<sup>27, 39, 54</sup>

*Abnormalities of Form:* Abnormalities in the size and shape of individual waves or in the relation of one wave to another can be detected by all ballistocardiographs, whether they can be calibrated or not. Qualitative deviation from the normal can be recognized at a glance. The absence or great reduction of any wave, its flattening or notching, or a disturbance of the normal relationship between waves, such as the equality of H and J, should be noted as abnormal.

While the abnormality of a single systolic complex may be easily and briefly described, that of the record as a whole is much more difficult, because abnormalities of form are prone to change from beat to beat with the respiratory cycle. If the respiratory cycles are put one below another, it becomes apparent that complexes occurring in similar positions in this cycle are identical. The procession of identical abnormal complexes with which electrocardiographers are so familiar is seen in ballistocardiograms only if respiration is suspended. Records taken during normal breathing often show one or more of the smaller complexes of the respiratory cycle to be abnormal in form, while the larger remain normal. Indeed, any proportion of the complexes of a respiratory cycle may be found abnormal, the rest remaining normal. But abnormality of the large complexes, the small ones remaining normal, is practically never seen.

Mayock and I, judging single complexes,<sup>39</sup> attempted to arrange the many varieties of abnormal forms in order of their importance, and Brown et al.<sup>3</sup> have made a useful classification based on the more general appearance of the record. While we need much more knowledge about the significance of the various types, in terms of the severity of the cardiac abnormality, several things can be said with reasonable confidence, and I will give my present viewpoint.

As the heart weakens, I expect the first effect to be seen in the smallest complexes of each respiratory cycle. As the heart weakens further, I expect the abnormality to spread to adjacent complexes until all are affected. The abnormality of form of a single complex in each cycle, often seen in healthy oldsters, seems not to be of great practical importance; but as the percentage of abnormal complexes rises an increasingly serious view of the situation should be taken.

This early involvement of the smallest complexes of the respiratory cycle seems a beautiful example of Starling's law of the heart, the weakening heart first contracting abnormally at the point in the respiratory cycle where it is most poorly filled. With this in mind, I am greatly interested in Brown's

suggestion<sup>2</sup> that coronary heart disease can be diagnosed by the abnormal relation between the size of the largest and smallest complexes of the respiratory cycle. I would expect this to be the case, but there is a practical difficulty with such a test, for many healthy persons, by overventilating voluntarily, can produce a ratio between the largest and smallest complexes which is abnormal by Brown's standards.<sup>3</sup> So those attempting to diagnose cardiac disease by this method will have to use great care about the emotional state of their subjects, who, if in apprehension or excitement, may give a ballistocardiogram which might be interpreted as indicating cardiac abnormality when the abnormal ratio was altogether due to overbreathing.

I shall not attempt to describe further the great variety of abnormal ballistic patterns that one sees chiefly in cases of manifest heart disease, but I can properly record two impressions which may be of some help in judging the severity of the dysfunction. My experience suggests that diminution of the I wave alone is the least serious of the abnormalities of form and, at the other extreme, that distortion of the record so great that the location of systole cannot be decided with certainty without a simultaneous electrocardiogram or pulse record should be regarded as indicating extremely serious myocardial dysfunction; so, in general, I agree with Brown's criteria.<sup>4</sup>

*Changes Due to Aging:* The pronounced changes due to aging<sup>22, 23</sup> are one of the most interesting facts about ballistocardiograms. As age advances the amplitude becomes smaller, the I and J waves diminishing in size relative to H and K even though health commensurate with one's age is maintained.<sup>23</sup> In some older persons, especially in those over 60 years of age, ballistic deterioration is unusually great, and the contour of the smaller complexes is sometimes found to be abnormal despite negative findings in the routine cardiac examinations, and despite the belief that they are in good health. This is an extraordinarily interesting group because, after my series had been followed for from eight to 10 years, when their records were arranged according to size and normality of contour of the ballistocardiogram a line could be drawn below which almost 50 per cent of the cases developed serious heart disease in the years following.<sup>40</sup> And many doctors have told me of cases in their own experience, cases with abnormal ballistocardiograms when the routine clinical examination was negative who subsequently developed cardiac disease or were the victims of sudden death. Nevertheless, it is the cases who do badly that are likely to be brought to one's attention, while those who do well must be ferreted out. This follow-up work must be greatly extended, to see if my experience is the usual experience and to teach us to distinguish better between serious and unimportant abnormalities of form.

I have also had in my series of healthy subjects two instances in which unquestioned attacks of coronary infarction occurred in persons who had had perfectly normal ballistocardiograms within two years before that event.

Interestingly enough, both these attacks followed most unusual effort; one of these cases (H. C. B.) has been reported in detail.<sup>22</sup>

Because of the marked effects of aging, many persons over 50 years of age have records which indicate abnormally weak hearts if healthy young adults are taken as the standard.<sup>22</sup> Many doctors find this disconcerting, especially if the older person gives no other evidence of ill health. But I have little doubt that tests of the voluntary muscles would show similar diminution of strength as age advances, although I am not aware of any data on the subject. That most older persons have weaker hearts than young ones should occasion no surprise; the interesting thing is that some maintain the youth of their hearts so much longer than do others.

This seems a proper place to report the final outcome of one of the cases of our 10 to 14 year follow-up study on whom judgment was deferred when the last report<sup>22</sup> was made. In this paper<sup>23</sup> we wrote: "Two other persons in our series have also developed ill health of a doubtful character together with marked deterioration of their ballistocardiograms. We have decided to await developments before reporting their cases in detail." This is the final report on one of these two.

#### CASE REPORTS

*Case 1.* K. L. T., a physician and professor, was 52 years of age and considered himself to be in good health when the first ballistocardiogram was taken in 1937. Since childhood he had suffered from occasional attacks of syncope on emotional stress, such as the drawing of blood. He had had allergic asthma in childhood but had outgrown it. Ever since severe dysentery in childhood he had had a tendency toward loose stools. He had occasional attacks of migraine, often with scotoma, and his hands tended to blanch unduly in cold weather. The first ballistocardiogram, shown in figure 3, was altogether normal.

In 1938 he had a "sensation of weakness in one arm" and was examined by Dr. T. G. Miller, who could demonstrate no abnormality of importance. Dr. Miller recorded the heart as of normal size, and noted no murmurs.

In 1941 the subject had an attack of renal colic and was operated upon; a ureteral calculus was found and removed, and he made a good recovery.

In April, 1944, he had another attack of renal colic and x-ray showed a stone in the left ureter, which was passed. A week after this he came to Dr. Miller for a check-up. Dr. Miller now noted a blowing systolic murmur at the apex with definite transmission to the left, and thought the heart was "possibly just a little widened to the left" by percussion. Blood pressure was 120 mm. Hg systolic and 70 mm. diastolic.

In June, 1945, he had a severe attack of lower sternal pain and became nauseated and vomited. Dr. Miller now found a mass in the gall-bladder area with tenderness, and suspected a gall-bladder attack. An electrocardiogram was negative. This attack subsided promptly, and he was not studied further.

In March, 1949, a second ballistocardiogram was secured in the course of studies on exercise<sup>27</sup> being conducted by Dr. Donald Makinson. The subject was asked to take part in these with the thought that he was altogether normal but the resting record (figure 3) was far from normal. Very few completely normal complexes



were seen, at most only about two out of the 10 of each respiratory cycle being normal in form.

On February 22, 1950, Dr. Miller being out of town, the subject consulted Dr. F. C. Wood because of another attack of substernal pain which had lasted for 25 minutes that morning. He now gave a history during the past year of slight substernal pain on effort or excitement, which stopped when effort stopped; the subject attributed this to esophageal spasm, from which he had suffered at intervals for some time.

He was at once admitted to the hospital, where physical examination disclosed a harsh systolic murmur at the apex and another at the base. Blood pressure was 135 mm. Hg systolic and 80 mm. diastolic. The heart was somewhat enlarged by orthodiagram. Sedimentation rate was normal, and a series of electrocardiograms on February 22, 23 and 28 was negative. No tenderness was reported over the gall-bladder. Coronary heart disease was suspected but the diagnosis was not regarded as established. The patient was discharged in a few days and, despite advice to the contrary, promptly resumed his usual way of life.

In April 1951 he had a third ballistocardiogram (figure 3) as part of our follow-up series.<sup>22</sup> This again was very abnormal; no normal complexes were seen; there were marked variation of form from beat to beat and a complete disappearance of the I wave in many complexes.

After this he worked steadily and effectively as a collaborator of the author, and neither complained of his health nor sought medical advice. His family concur with the thought that he seemed in good health, but they thought he had slowed up.

On March 29, 1952, he attended a wedding and decided to walk home alone instead of going to the reception. He walked about three miles, the last uphill, and was found dead on the sidewalk at this point. A boy is reported to have seen him collapse. There was no evidence of trauma to the body which suggested an accident. No necropsy was performed.

In contrast to this case, in which a deterioration of the ballistocardiogram was followed by sudden death, I shall also report on one in which a normal ballistocardiogram was followed by more years of life than most would have expected from the severity of the clinical picture.

*Case 2.* J. B. was 27 in 1938 when he first entered the hospital. He gave a history of rheumatic fever in childhood and had physical signs characteristic of mitral stenosis and insufficiency. The electrocardiogram showed auricular fibrillation. The orthodiagram was reported as follows: "The heart is enormously enlarged (274 per cent above the predicted normal area); the enlargement involves all chambers but particularly the left auricle, which is hugely dilated."

To our great surprise the ballistocardiogram, while confirming the diagnosis of auricular fibrillation, was otherwise negative. It is shown in figure 4.

A final report cannot be made because, at the time of writing, June, 1952, the patient is still alive. He has had many admissions to the hospital, and repeated x-ray studies have confirmed the first finding. He has been in congestive failure several times in recent years, requiring vigorous therapy to keep him comfortable and free of fluid. His ballistocardiogram has deteriorated somewhat but is still rather better than the alarming cardiac findings would lead one to expect.

How many readers would have given him 14 years of life on the basis of the routine study in 1938?



## UTILITY

I will now try to answer the question in the minds of so many: "What are these records worth as a practical proposition?" You must not expect too clear an answer from me, for this subject is still in its infancy, and before attempting any answer at all it seems wise to discuss the problem in its broader aspects.

In considering the utility of any diagnostic tool one must keep in mind that the ultimate purpose of medicine is the prevention and cure of disease, and that a diagnosis is useful to the patient only if it contributes to this end. To discover something about the patient and give it a name is an advance, but of itself it is not enough. Let us also keep in mind that the information given by the ballistocardiograph is physiologic in nature rather than anatomic or descriptive.

Doctors are accustomed to employ diagnoses which differ greatly in meaning and significance, and the several types should be clearly distinguished. For example: Angina pectoris is a descriptive diagnosis; it describes certain sensations of the patient; around it a clinical picture has been built up. Coronary sclerosis is a pathologic and anatomic diagnosis, to be established with certainty only at necropsy. For many years diagnoses based on these two aspects of clinical medicine, the descriptive and the pathologic, were the center of interest and attention. Recently, with the rise of the physiologic school in clinical medicine, we have had increasing interest in diagnosing abnormalities of another type. The ballistocardiogram provides new information of this kind, giving evidence concerning a physiologic function, the strength or weakness of the heart's beating.

The relation between the symptoms, the anatomic lesions and the physiologic aspects of disease is obviously a matter of great interest and importance. It was a great advance to realize that angina pectoris was generally accompanied by coronary sclerosis. But one must not expect that complete correspondence between diagnoses of the various types will be found. For example, angina pectoris is not always associated with obstructive coronary lesions, as in anemia, and an attempt to infer the absence of anatomic coronary arteriosclerosis<sup>41</sup> from the absence of the symptoms of angina pectoris would lead to a poor score indeed. Obviously, the two aspects of disease represented by angina pectoris and coronary sclerosis are related, but not closely so.

Similarly, physiologic abnormality of the cardiac contraction, judged by the ballistocardiogram, usually accompanies the symptoms of chronic angina pectoris, and doubtless the lesions of generalized coronary sclerosis<sup>39</sup> also, but one must not expect the relationship to be invariable. Ballistic abnormalities accompany the symptoms of angina pectoris much more frequently than do abnormalities of the electrocardiogram.<sup>42</sup> Nevertheless, a considerable number of cases having typical angina or infarction have nor-

mal ballistocardiograms when tested at rest.<sup>28</sup> Figure 4 gives a striking example. This should occasion no surprise.

By experience with more accessible parts of the body, we know how much pain a tiny lesion may cause, and it is proper to imagine severe angina caused by a coronary lesion depriving only a minute part of the heart of its needed blood supply, while the rest of the heart, unaffected, contracted normally. Similarly, a cardiac infarct might involve only a small percentage of the ventricular mass, and the rest contract normally. In accord with this conception is the fact that the combination of clinical evidence of coronary heart disease and a normal resting ballistocardiogram is usually found in patients much younger than the larger group having both evidence of coronary heart disease and highly abnormal ballistocardiograms.<sup>42</sup>

Figure 4 shows records from two cases with undoubted angina; their ballistocardiograms could hardly be more different, and one is altogether normal in form. In these two cases the anatomic lesions were probably quite different, and this would have been suspected by a careful clinician without a ballistocardiogram; I have reproduced the record of J. J. for that reason. But in many cases of angina the ballistocardiogram indicates differences in cardiac performance of which the routine clinical study gives no clue. Such differences, as well as the complete dissimilarity between the records of the two cases of angina pectoris shown in figure 4, emphasize the point I wish to make: The purpose of taking a ballistocardiogram on a case of angina pectoris is not so much to assist in establishing that diagnosis as to provide information of a new kind about the heart of the patient concerned.

There is an interesting similarity between the increasing frequency of ballistic abnormalities as age advances and the increasing incidence of coronary arteriosclerosis found at necropsy at corresponding ages. The absolute figures vary, for in our first series<sup>29</sup> we accepted as normal many records we would not pass now. But in all series<sup>28, 29, 42, 49, 51, 52</sup> the percentage of abnormal ballistocardiograms, negligible in young adults, increases steadily as age advances to at least the sixth decade; after this it remains about constant in some series and continues to increase in others. An almost exactly similar statement can be made about the frequency of arteriosclerosis at necropsy as age advances.<sup>41</sup> Also, among our cases who, having abnormal ballistocardiograms during life, later came to necropsy, coronary heart disease was the most frequent finding.<sup>39</sup> If those dying of rheumatic heart disease and of neoplasms are excluded, coronary arteriosclerosis stands quite alone in importance. Obviously, therefore, abnormal ballistocardiograms and coronary heart disease are closely associated, but we must not expect that the relation will be invariable. Physiologic functions like those measured by the ballistocardiogram are very variable and may be influenced by such factors as food, exercise, emotion, drugs and the like. The administration of digitalis may convert an abnormal ballistocardiogram to a normal one,<sup>28, 54</sup> or, indeed, if unwisely given, cause marked deterioration in

the record.<sup>28</sup> A surgical operation, especially if on the heart itself, may cause marked deterioration of the record for a while; figure 5 gives an example. Then there is the interesting and rather puzzling observation that some weakened hearts, if stimulated by a situation requiring greater cardiac effort, like the upright position<sup>29</sup> or mild exercise,<sup>17</sup> may, as it were, pull themselves together and give a more normal performance. But in any event, a multitude of physiologic factors alter the strength of the heart's beating and so affect the ballistocardiogram without having any effect on the anatomic lesions of the heart. Certainly complete correspondence between physiologic performance and anatomic lesions is not to be expected; other important factors enter into the situation.

One is stimulated to the physiologic study of many diseases by the realization of the inadequacies of the anatomic and descriptive diagnoses in terms of the main interest of the patient. Suppose one does suffer from angina pectoris, what does it mean to him? We know well that some such cases "fall down and perish almost immediately"; but apparently this is true of only a small minority, and all of us know of many persons so diagnosed who have lived long and useful lives, somewhat handicapped as to extreme exertion, it is true, but not sick in the usual sense of the word. Certainly the diagnosis of angina pectoris does not automatically convey an accurate prognosis, and we still have much to learn about its therapy. New and pertinent information about the functioning of the hearts of patients with this disorder is certainly to be welcomed. With the ballistocardiogram before one, cases of angina divide themselves into several groups according to their myocardial performance. Looking into the future, it will be a fascinating business to follow these cases and determine the prognostic value of the record, to try both new and old remedies aimed at bettering the functional abnormality indicated by the ballistic record, using this record to help to determine the success or failure of the effort at therapy. Concentrating on the present and on the facts at hand, the ballistocardiogram demonstrates clearly that the two cases whose records are reproduced in figure 4, although both are properly diagnosed angina pectoris, differ profoundly, for, while the interpretation of the record in terms of cardiac function is a theory, it is a fact that the cardiac contraction moved the body of one patient with a force far larger than was manifested by the other; for in both cases the ballistocardiograph's spring, of known strength, was bent a known distance in a known time, with a rhythm similar to that of the heart.

Let me illustrate further the physiologic viewpoint by asking you to consider the kind of information given by the estimate of blood pressure, another physiologic method most useful in the clinic. As is well known, there are changes in blood pressure which characteristically accompany hyperthyroidism, aortic regurgitation and brain tumor, and so aid in the diagnosis of these conditions. Nevertheless, the chief contribution of the blood pressure estimate has been, not to assist in the diagnosis of anatomic lesions, but to open up an entirely new clinical field, the field of hypertension

and shock, about which doctors had been largely ignorant before the estimate was introduced.

I wish readers to think of the ballistocardiogram similarly; it may be of some help in diagnosing things which are now familiar, such as coronary heart disease, hyperthyroidism, myxedema, aortic regurgitation, patent ductus and coarctation of the aorta, etc., but its chief field is to open up new aspects of cardiovascular disease, aspects concerned with strength and weakness of the heart, aspects about which the present routine clinical study gives very little information.

I recently had occasion to read the authoritative articles on cardiac disease, written mostly by members of this College, and just published in the new edition of Nelson's Loose-Leaf Medicine. In these I encountered with great frequency terms such as "gradual weakening of the myocardium," "heart failure," "cardiac fatigue," "myocardial weakness," "stage of diminished cardiac reserve." In the light of the ordinary clinical study the conceptions characterized by such terms are little more than pure speculations. With the ballistocardiogram before one they at once acquire meaning; one begins to look at one's cases in a new way, and to make distinctions not possible before.

Thus by means of ballistocardiograms one finds that most older people with the clinical syndrome of chronic angina have abnormal ballistocardiograms<sup>38,42</sup> and so diminished myocardial function, even though the present routine clinical study is often negative.

One finds that in many cases of acute myocardial infarction, myocardial function is hard hit, the ballistocardiogram becoming extremely abnormal<sup>38</sup>; but in other cases of cardiac infarction, usually a younger group, the ballistocardiogram remains normal, or nearly so, causing one to suspect that the damage was localized to a small area. In some cases of infarction the ballistocardiogram indicates myocardial recovery as time passes; in others, alas, it remains highly abnormal<sup>38</sup>; and is not this difference worth knowing when one is attempting to assess the patient's working capacity after the acute stage is over?

One finds that in most cases of hypertension the ballistocardiogram is either normal in size or unduly small, evidence in accord with the current view that the physiologic abnormality of such cases is increased peripheral resistance. But one also finds cases in which a hypertension is accompanied by an abnormally large ballistocardiogram, the combination of events seen in healthy persons after an injection of adrenalin.<sup>37</sup> Obviously a sharp distinction can be easily made between cases of hypertension, and it is my present impression that the emotional hypertensions and those due to pheochromocytomas will fall into the latter group, the more common types into the former.

One finds most cases of hyperthyroidism to have ballistocardiograms abnormally large but normal in form, but one also finds some cases with small distorted records, and then it seems evident that thyroid heart disease

has made its appearance, and this can occur while other cardiac studies are still negative.

By taking records before and after a trial of therapeutic measures, their success or failure can be evaluated. Digitalis often causes startling improvement in the record,<sup>43, 55</sup> but by no means always. Abdominal binders help the circulation of some people<sup>3</sup> but not that of others; penicillin and other measures given to a case of luetic heart disease were followed by a startling improvement in the ballistocardiogram in one of our cases (figure 4). The modern surgical cardiac operations usually cause marked deterioration in myocardial function as an immediate postoperative effect, but this is recovered from and the final result is often gratifying improvement of myocardial power (figure 5).

Detrimental factors can also be sought, and smoking causes real deterioration in the ballistocardiograms of certain people, as Dr. Dock<sup>48</sup> and the Drs. Mandelbaum<sup>44</sup> have pointed out; this has been confirmed by Dr. C. B. Henderson in my laboratory.<sup>45</sup> The question whether these patients would be benefited by omitting tobacco becomes immediately pertinent.

If the ballistocardiogram fails to increase in amplitude after exercise, or becomes abnormal in form, one can believe that the cardiac reserve is exhausted with a confidence not possible (at any rate not to me) from such evidence as increased breathlessness on exertion, which may be due to pulmonary abnormality or anemia and not to myocardial weakness at all.

The average ballistocardiogram changes markedly as age advances, but in individuals the change is not uniform.<sup>28</sup> I can make a fair guess at a man's decade of life by inspecting his record. But the hearts of some persons appear to get old before their time, while those of others maintain their youth despite advanced chronologic age. In cases of the former type the ballistocardiogram often becomes abnormal in later life without simultaneous manifestation of ill health,<sup>28, 47, 53</sup> and so the possibility of a preventive program must not be lost sight of. The old hopeless outlook about arteriosclerosis is being supplanted by increased knowledge derived from animal experiments, which certainly show that arterial lesions can regress under certain conditions. There are also interesting rumors concerning the reduced incidence of arteriosclerotic heart disease during periods of semi-starvation in Norway and Russia during the last war. While readers may not share my view—and I have no way to convince them if they do not—I feel sure that if my own ballistocardiogram unduly deteriorated without obvious cause, suspecting the slow development of coronary arteriosclerosis I would certainly stop smoking and probably go on a very low fat diet. The difficulty of establishing the effectiveness, or lack of it, of such a preventive program is well known, but the time has come to think about such matters, and the ballistocardiogram could be readily used as a screening test.

In conclusion, all the evidence suggests that in the ballistocardiogram we have readily available a new kind of information intimately related to cardiac strength and weakness, words hitherto much bandied about by

physicians on the basis of evidence of a most indirect kind, but always recognized as representing an aspect of heart disease of primary importance, knowledge of which would most certainly be useful in the handling of our patients.

#### ACKNOWLEDGMENT

I am indebted to Dr. T. G. Miller and Dr. Francis C. Wood for access to their records to obtain information used in the report of case I.

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## A STUDY OF THE BENEFICIAL EFFECTS OF ANTICOAGULANT THERAPY IN CONGES- TIVE HEART FAILURE\*

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THROMBOEMBOLI are a frequent cause of death in patients with congestive heart failure. In 565 patients with rheumatic heart disease and congestive heart failure, autopsied at the Los Angeles County Hospital,<sup>1</sup> thromboemboli were found in 30.3 per cent. In 114 patients thromboemboli were the direct cause of death, in 20 patients a contributory cause of death, and in 28 patients did not contribute to death. Despite this fact, anticoagulants have not been widely used as an adjuvant to routine therapy. Several groups<sup>2a, b, 3, 4</sup> have studied this problem and report a 5.8 to 8 per cent reduction in mortality, and from 6 to 9 per cent reduction in thromboemboli in those patients treated with Dicumarol.

In the present study, 629 patients with congestive heart failure have been observed. A preliminary report of the first 300 patients has been presented by Levinson and Griffith.<sup>5</sup> Dicumarol, Tromexan,<sup>§</sup> Depo-Heparin\*\* and Dicumarol with Depo-Heparin or Sodium Heparin have been studied.

The benefit of anticoagulants through reduction of mortality and thromboemboli is in this study twice that reported previously.

### METHODS

During the first year of this study, all patients with congestive heart failure admitted to the medical wards of the Los Angeles County Hospital were serially allocated to control, Dicumarol treated and Depo-Heparin treated groups. The routine therapy of the cases was handled by the regular hospital staff, and anticoagulant therapy was personally directed by one of the investigators (D. C. L.). During the second year of the study, all patients with congestive heart failure admitted to the medical floors of the

\* Presented at the Thirty-third Annual Session of the American College of Physicians, Cleveland, Ohio, April 23, 1952.

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Aided by grants from the Upjohn Company, Geigy Pharmaceuticals and the Los Angeles Heart Association.

† Trainee of the National Heart Institute 1950-51.

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§ Tromexan kindly furnished by Geigy Pharmaceuticals, 220 Church St., New York City.

\*\* Depo-Heparin kindly furnished by the Upjohn Co., Kalamazoo, Michigan.

hospital were treated in a conventional manner. On certain designated wards, the patients were used as controls and did not receive anticoagulants. The remaining wards were each assigned specific anticoagulants, and patients admitted to these wards received anticoagulant therapy according to a rigidly defined schedule. The anticoagulants used were (1) Dicumarol, (2) Depo-Heparin, (3) Tromexan, (4) Dicumarol and Depo-Heparin, and (5) Dicumarol and Sodium Heparin. The anticoagulants were administered by the regular hospital staff. During both years the patients were seen and examined frequently by the investigators.

Anticoagulant therapy was instituted by the regular hospital staff as soon after admission as possible. In the case of Heparin and Depo-Heparin, immediate institution of anticoagulant therapy was obtained. When Tromexan and Dicumarol were used, therapy was not instituted until a pretreatment prothrombin determination was obtained. Occasionally this resulted in a 24 hour delay in the institution of anticoagulant therapy. Patients were occasionally encountered, in all groups, with hypoprothrombinemia of 50 per cent or less on admission. These patients were excluded from the series. Anticoagulant therapy was continued until the patient was ready for discharge or free of congestive heart failure.

The patients receiving Depo-Heparin or Heparin were followed by clotting times performed by the three-tube Lee-White<sup>6</sup> method. Depo-Heparin and Heparin dosage was generally regulated by the results of the clotting times. In most instances an initial dose of 400 mg. of Depo-Heparin was found to be optimal. Maintenance dosage was usually 200 mg. every 20 hours. Sodium Heparin was almost uniformly effective when given intramuscularly in a dose of 50 mg. every four hours.

Prothrombin determinations were done in the anticoagulant research laboratory of the Department of Cardiology. During the first year Quick's method,<sup>7</sup> using Difco thromboplastin, was employed. During the second year, the method of Ware and Stragnell<sup>8</sup> was used. This method is a modification of Owren's method,<sup>9</sup> and involves dilution of the unknown plasma and the addition of an aliquot of prothrombin-free beef plasma. A stable, dried, easily reconstituted prothrombin standard is tested concomitantly with the unknown plasma and from the results obtained on serial dilution of the prothrombin standard an activity curve is constructed. The stable prothrombin standard provides a reproducible reference point. The errors inherent in the Quick procedure apparently are eliminated in this method.

Dicumarol dosage was regulated by daily prothrombin determinations so as to maintain a prothrombin level at or near 20 per cent of normal. In general, patients with congestive heart failure were found to be more reactive to Dicumarol than those without congestive heart failure. The response of the individual patient was fairly constant, but the pattern from patient to patient varied considerably. The following dosage schedule served as a guide.

Initial Dose	Prothrombin 75-100%	200 mg.
	50-75%	125-150 mg.
Maintenance	Prothrombin	
	less than 15%	none
	15-25%	25-50 mg.
	25-35%	50-75 mg.
	35-45%	75-125 mg.
	45-60%	125-200 mg.
	above 60%	200-300 mg.

Rapid fluctuation of the prothrombin level encountered with Tromexan made it advisable to obtain two prothrombin determinations daily, the first in the early morning and the second in the afternoon.\* From the direction of change of the prothrombin level, one of the following dosage schedules was recommended.

Initial Dose	Prothrombin	75-100%	900-1200 mg.
		50-75%	600-900 mg.
Maintenance	Prothrombin	Level Falling	Level Rising
	10-20%	none	300 mg.
	20-30%	300 mg.	450 mg.
	30-40%	450 mg.	600 mg.
	40-50%	600 mg.	750 mg.
	50-75%	750 mg.	900 mg.
	above 75%	900 mg.	1200-1500 mg.

During the first few months Tromexan was given in a single dose after the afternoon prothrombin determination was available. Considerable variation in response and wide fluctuations were encountered with this dosage schedule. More reproducible and stable results were obtained by giving the drug in divided dosage, one-half in the afternoon and one-half 12 hours later.

When Dicumarol with Depo-Heparin or Sodium Heparin was given, Dicumarol was given according to the schedule noted above, and therapy with the Heparin drug was initiated immediately upon entry and continued only until the prothrombin level fell below 30 per cent. If the prothrombin level subsequently rose above 30 per cent, the Heparin drug was reinstituted, in most instances.

The maintenance level of hypoprothrombinemia is arbitrarily defined as the lowest level which was maintained, without a 10 percentile deviation of more than one day's duration. For example, if a patient had an initial prothrombin level of 90 per cent, which by the third day fell to a level of 12 per cent, and remained within the 10 to 20 per cent range, with one determination on the sixth day of 27 per cent, and on the seventh day was again in the 10 to 20 per cent range, the patient was classed as maintained between 10 and 20 per cent. If this patient had a prothrombin level of 27 per cent on two consecutive days (say, the sixth and seventh) and the remainder of the time was held between 10 and 20 per cent, he was then classed as being maintained between 20 and 30 per cent, since the elevation of one 10 percentile occurred

\* Blood for the afternoon prothrombin determinations was usually drawn between 2:00 and 3:00 p.m., and the results were routinely available by 4:30 p.m.

on two days. If the same patient on the sixth day had a level of 35 per cent, and the remainder of the time was maintained at the 10 to 20 per cent range, the patient was classed as being maintained at the 30 to 40 per cent level, since the elevation exceeded one 10 percentile on that one day.

All of the patients included had either right-sided failure or combined right- and left-sided failure. Patients with pure left ventricular failure were not included. Etiologic diagnosis was based on clinical history, physical examination and electrocardiographic findings. Five etiologic groupings were used: rheumatic heart disease (RHD), hypertensive heart disease without evidence of coronary artery disease (HHD), coronary artery disease without hypertension (ASHD), hypertensive heart disease with evidence of coronary artery disease (HASHD), and miscellaneous heart disease, including cor pulmonale, luteic heart disease and congestive heart failure secondary to arteriovenous aneurysm.

All patients whose fundamental rhythm originated from a focus other than the sinus node were classed as having an arrhythmia. Any patient who had had a thromboembolic episode immediately preceding entry to the hospital was excluded from the study. All of the patients considered were hospitalized for at least 72 hours. If a patient was discharged or died in a shorter period of time, he was excluded from consideration. The duration of hospitalization was defined as the length of time the patient was hospitalized because of congestive heart failure only.

Hemorrhage in the patients studied was classed as major or minor. Major hemorrhage included serious bleeding from any site, such as gastrointestinal, genitourinary, central nervous or pulmonary system. Minor hemorrhage included such things as ecchymosis, petechiae, microscopic hematuria and epistaxis. When hemoptysis occurred in conjunction with the signs of pulmonary embolism and infarction it was not classed as hemorrhage.

For purpose of tabulation, deaths from any cause and nonfatal thromboembolic episodes were termed "unsatisfactory results." The following were defined as thromboembolic episodes: coronary occlusion with myocardial infarction, peripheral artery thrombosis or embolus, thrombophlebitis or phlebothrombosis, pulmonary infarction, cerebral vascular accident in which no evidence of hemorrhage could be recognized. Patients who appeared to be responding to therapy and died suddenly, in whom autopsy was not obtained, were classified, in both the control and treated groups, as fatal thromboembolic episodes. In three such instances of sudden death, autopsy found cerebral hemorrhage to have caused death, and these three were not, therefore, classified as thromboembolic episodes. Two clinically unsuspected thromboemboli were found at autopsy, and these patients were classified on the basis of the necropsy report.

A few patients in the first year's series did not fulfill all the criteria outlined and they have been excluded from this report.

TABLE I  
Distribution of Patients in Treated and Control Groups

	RHD				HHHD				ASHD				HASHD				Misc.				Total			
	Control		Treated		Control		Treated		Control		Treated		Control		Treated		Control		Treated		Control		Treated	
	S	UnS	S	UnS	S	UnS	S	UnS	S	UnS	S	UnS	S	UnS	S	UnS	S	UnS	S	UnS	S	UnS	S	UnS
Male	16	10	26	4	35	8	77	11	8	70	4	12	4	11	1	8	0	14	2	102	30	198	22	22
Female	14	8	58	2	28	4	56	7	10	3	24	3	6	3	15	2	2	3	0	60	21	156	14	14
White	27	16	78	6	49	9	103	17	37	10	84	7	15	6	21	3	8	3	15	2	136	44	301	35
Colored	3	2	6	0	14	3	30	1	4	1	10	0	3	1	5	0	2	0	2	0	26	7	53	1
Regular rhythm	12	7	24	2	48	8	95	11	27	7	63	2	9	4	14	0	9	3	16	2	105	29	212	17
Arrhythmia	18	11	60	4	15	4	38	7	14	4	31	5	9	3	12	3	1	0	1	0	57	22	142	19
P.H.T.E.	4	3	19	1	6	1	8	1	14	2	38	3	8	3	10	1	1	0	1	0	33	9	76	6
No P.H.T.E.	26	15	65	5	57	11	125	17	27	9	56	4	10	4	16	2	9	3	16	2	129	42	278	30
P.H. failure	22	14	63	5	29	7	68	11	21	7	42	5	11	4	13	2	6	2	12	1	89	34	198	24
No P.H. failure	8	4	21	1	34	5	65	7	20	4	52	2	7	3	13	1	4	1	5	1	73	17	156	12
Age	8	2	26	1	0	0	2	0	1	0	1	0	0	0	0	0	1	0	1	0	10	2	30	1
20-40	16	8	41	5	21	1	39	2	4	4	15	1	2	0	2	0	4	2	9	1	47	15	106	9
41-60	6	8	17	0	35	10	82	13	29	7	63	4	12	6	21	2	5	1	5	1	87	32	188	20
61-80	0	0	0	0	7	1	10	3	7	0	15	2	4	1	3	1	0	0	2	0	18	2	30	6
80																								
Hospital stay, days	12	5	31	2	31	3	63	9	17	5	47	2	2	12	2	4	0	4	1	66	15	157	16	16
4-7	14	6	34	3	22	5	49	7	10	4	35	4	10	4	13	1	4	2	9	1	60	21	140	16
8-14	2	4	11	0	7	4	17	2	8	2	10	1	4	1	0	0	1	0	3	0	22	11	41	3
15-21	0	1	6	1	2	0	4	0	2	0	1	0	2	0	1	0	1	0	1	0	7	1	13	1
22-28	2	2	2	0	1	0	0	0	4	0	1	0	0	0	0	0	0	1	0	0	7	3	3	0
28+																								
Total	30	18	84	6	63	12	133	18	41	11	94	7	18	7	26	3	10	3	17	2	162	51	354	36

S = Satisfactory result.  
UnS = Unsatisfactory result.

P.H. = Past history.  
T.E. = Thromboembolism.

## RESULTS

From table 1 it is apparent that the distribution of patients in the control and treated groups is essentially the same with respect to sex, race, age and duration of hospitalization. Table 1 also indicates the effect of cardiac rhythm, past history of thromboemboli and past history of congestive failure on the outcome. Statistical analysis of these data \* showed that in neither the control nor the treated group did the presence of an arrhythmia, a past history of congestive failure or a past history of thromboembolism significantly affect the outcome.

Thirty-one per cent of the controls had "unsatisfactory results," as compared to 10 per cent of the treated group. This represents a statistically significant reduction in the "unsatisfactory results" observed in the treated

TABLE II  
Distribution of Patients Treated with Various Anticoagulants. Patients receiving Dicumarol and Depo-Heparin or Sodium Heparin are grouped together.

Agent	RHD		HHD		ASHD		HASHD		Misc.	
	Satisfactory	Unsatisfactory	Satisfactory	Unsatisfactory	Satisfactory	Unsatisfactory	Satisfactory	Unsatisfactory	Satisfactory	Unsatisfactory
Dicumarol	40	1	39	5	22	0	7	2	4	0
Depo-Heparin	25	2	44	3	25	3	9	1	6	1
Heparin and Dicumarol	6	2	25	4	22	4	5	0	2	0
Tromexan	13	1	25	6	25	0	5	0	5	1
Total	84	6	133	18	94	7	26	3	17	2

patients as compared with the controls. The patients with rheumatic heart disease (RHD) and coronary artery disease without hypertension (ASHD) showed the most significant improvement. Older patients with rheumatic heart disease were particularly benefited. In the hypertensive group with coronary artery disease (HASHD) and in the miscellaneous group an observed decrease in "unsatisfactory results" was noted which was not statistically significant. In the hypertensive group without evidence of coronary artery disease, no change in "unsatisfactory results" was noted under treatment.

In table 2 the distribution of patients with regard to anticoagulant agents is shown. No significant difference can be found between the various agents.

Table 3 contains brief summaries of patients classified as "unsatisfactory results," e.g., of the fatal cases and those who had thromboemboli.

\* The statistical tests used were chi square and expansion of the binomial theorem. A p value of 0.01 or less represented a statistically significant finding.<sup>10</sup>



TABLE III  
Unsatisfactory Results  
*Rheumatic Heart Disease*

No.	Group	Age Color Race	Rhythm	P.H.T.E.	Fail- ure	Comment
1	Control	38 W M	AF	0	+	Good response to treatment of failure. On 4th day chest pain, hemoptysis and x-ray evidence of pulmonary infarction. Patient recovered.
2	Control	41 C F	RSR	0	0	Good response to treatment of failure. On 11th day sudden hematemesis, melena and death. No autopsy.
3	Control	68 W M	RSR	0	+	Poor response to treatment of failure. CVA on 5th day. Died on 7th day. No autopsy.
4	Control	68 C M	AF	0	+	Poor response to treatment of failure. Died on 30th day. Autopsy: subacute myocardial infarct and thrombosis in right atrial appendage.
5	Control	70 W F	AF	0	+	Slow response to treatment of failure. Suddenly died on 8th day. No autopsy.
6	Control	67 W M	RSR	0	0	Fair response to treatment of failure. Intermittent episodes of dyspnea. Died on 10th day. Autopsy: multiple pulmonary infarcts.
7	Control	69 W M	AF	0	+	Fair response to treatment of failure. Sudden loss of consciousness and death on 16th day. No autopsy.
8	Control	46 W M	AF	0	+	Slow response to treatment of failure. CVA with left hemiplegia and death on 11th day. No autopsy.
9	Control	41 W F	AF	0	+	Poor response to treatment of failure. Died on 22nd day. No clinical evidence of T.E.
10	Control	45 W F	RSR	0	+	Good response to treatment of failure. Suddenly died on 6th day. Autopsy: massive pulmonary embolus.
11	Control	42 W M	AF	+	+	No response to treatment of failure. Died on 40th day. No autopsy. No clinical evidence of T.E.
12	Control	47 W F	AF	+	+	Fair response to treatment of failure. Sudden chest pain and dyspnea with x-ray evidence of pulmonary infarct on 17th day. Patient recovered.
13	Control	32 W F	RSR	0	0	Good response to treatment of failure. CVA on 8th day. Patient recovered.
14	Control	65 W F	RSR	0	+	Good response to treatment of failure. CVA and death on 10th day. No autopsy.
15	Control	58 W F	AF	+	+	Poor response to treatment of failure. Died suddenly on 4th day. Autopsy: multiple pulmonary infarcts.
16	Control	55 W M	RSR	0	+	Initial slow response to treatment of failure, then progressively downward course. Died on 20th day. Autopsy: congestive heart failure. No T.E.
17	Control	61 W M	AF	0	+	Little response to treatment of failure. Sudden death on 7th day. Autopsy: cerebral and pulmonary emboli.
18	Control	67 W M	AF	0	+	Good response to treatment of failure. Sudden chest pain, hemoptysis and death on 15th day. No autopsy.

TABLE III—Continued

No.	Group	Age Color Race	Rhythm	P.H.T.E.	Fail- ure	Comment
19	Dicumarol	34 W F	AF	0	0	Fair response to treatment of failure. Prothrombin 40-50%. Sudden convulsion and death on 7th day. Autopsy: cerebral embolus.
20	Depo-Heparin	50 W M	RSR	0	+	No response to treatment of failure. Adequate anticoagulant therapy. Died on 10th day. Autopsy: congestive heart failure, no T.E.
21	Depo-Heparin	42 W M	AF	0	+	Slow response to treatment of failure. Adequate anticoagulant therapy. Intermittent chest pain, dyspnea and cough. Died on 11th day. Autopsy: multiple pulmonary emboli.
22	Dicumarol and Depo-Heparin	41 W M	AF	+	+	No response to treatment of failure. Prothrombin 10-20%. Died on 24th day. No autopsy. No clinical evidence of T.E.
23	Dicumarol and Depo-Heparin	52 W M	AF	0	+	Poor response to treatment of failure. Prothrombin less than 10%. Died on 8th day. No autopsy. No clinical evidence of T.E.
24	Tromexan	44 W F	RSR	0	+	No response to treatment of failure. Prothrombin less than 10%. Died on 5th day. Autopsy: necrotizing bronchopneumonia, no T.E.

*Hypertensive Heart Disease without Coronary Artery Disease*

1	Control	66 C M	RSR	0	+	Poor response to treatment of failure. Died on 7th day. Autopsy: pheochromocytoma, no T.E.
2	Control	78 W M	AF	0	+	Slow response to treatment of failure. Gradual coma and hemiplegia on 16th day. Died on 17th day. No autopsy.
3	Control	68 W M	RSR	0	0	Slow response to treatment of failure. Developed uremia and died on 11th day. Autopsy: small pulmonary embolus and thrombosis on left iliac vein.
4	Control	50 C M	RSR	0	+	No response to treatment of failure. Developed uremia and died on 15th day. No autopsy. No clinical evidence of T.E.
5	Control	81 W F	AF	0	+	Poor response to treatment of failure. Became comatose on 13th day. Died on 14th day. No autopsy. No clinical evidence of T.E.
6	Control	79 C M	RSR	+	0	Fair response to treatment of failure. CVA and died on 23rd day. No autopsy.
7	Control	62 W F	AF	0	+	Gradual response to treatment of failure. Died suddenly on 13th day. Autopsy: pulmonary infarct and thrombosis in right atrial appendage.
8	Control	75 W F	RSR	0	0	Fair response to treatment of failure. CVA and died on 9th day. No autopsy.
9	Control	73 W M	RSR	0	0	Poor response to treatment of failure. Developed uremia and died on 14th day. No autopsy. No clinical evidence of T.E.

TABLE III—Continued

No.	Group	Age Color Race	Rhythm	P.H.T.E.	Fail- ure	Comment
10	Control	79 W M	AF	0	+	No response to treatment of failure. Developed uremia and died on 19th day. No autopsy. No clinical evidence of T.E.
11	Control	67 W M	RSR	0	0	Fair response to treatment of failure. CVA on 4th day and died on 5th day. No autopsy.
12	Control	66 W F	RSR	0	+	Fair response to treatment of failure. Sudden coma and died on 4th day. Autopsy: extensive cerebral hemorrhage, no T.E.
13	Dicumarol	71 W F	RSR	0	+	Good response to treatment of failure. On 8th day prothrombin less than 10% and patient had a massive hematemesis. Given 100 mg. emulsified vitamin K <sub>1</sub> intravenously and 500 c.c. of blood. Patient responded, but eight hours later suddenly became cyanotic and died. No autopsy. Not classed as T.E.
14	Dicumarol	61 W M	RSR	0	+	Good response to treatment of failure. Prothrombin 20-30%. Ambulatory on 9th day when suddenly collapsed and died. Autopsy: pulmonary embolus.
15	Dicumarol	77 W F	AF	0	+	Poor response to treatment of failure. Prothrombin 30-40%. Became uremic and died on 22nd day. No clinical evidence of T.E.
16	Dicumarol	65 W F	AF	0	+	Slow response to treatment of failure. Prothrombin 10-20%. Developed uremia and died on 13th day. Autopsy: congestive heart failure, no T.E.
17	Dicumarol	81 W F	RSR	0	0	Poor response to treatment of failure. Prothrombin 10-20%. Developed bronchopneumonia and died on 7th day. No autopsy. No clinical evidence of T.E.
18	Depo-Heparin	75 C M	AF	0	0	No response to treatment of failure. Adequate anticoagulant therapy. Died on 7th day. Autopsy: congestive heart failure, no T.E.
19	Depo-Heparin	71 W M	RSR	0	+	Slow response to treatment of failure. Adequate anticoagulant therapy. Clotting time not unduly prolonged. Sudden coma and died on 8th day. Autopsy: intracranial hemorrhage, no other hemorrhage found, no T.E.
20	Depo-Heparin	72 W M	AF	0	+	Fair response to treatment of failure. Adequate anticoagulant therapy. Developed fever on 4th day and died on 6th day. Autopsy: bronchopneumonia, congestive heart failure, no T.E.
21	Dicumarol and Depo-Heparin	65 W F	AF	0	+	Initial good response to treatment of failure, then gradual downward course. Prothrombin 30-40%. Died on 19th day. No autopsy. No clinical evidence of T.E.

TABLE III—Continued

No.	Group	Age Color Race	Rhythm	P.H.T.E.	Failure	Comment
22	Dicumarol and Depo- Heparin	76 W F	AF	0	0	Poor response to treatment of failure. Prothrombin 40-50% (Depo-Heparin discontinued on 3rd day). Died on 13th day. No autopsy. No clinical evidence of T.E.
23	Dicumarol and Heparin	58 W M	RSR	+	0	No response to treatment of failure. Prothrombin 10-20%. On 5th day had pulmonary infarct and developed sudden hemiplegia. Died on 6th day. No autopsy.
24	Dicumarol and Heparin	82 W M	RSR	0	+	No response to treatment of failure. Prothrombin 30-40%. Developed uremia and died on 7th day. No autopsy. No clinical evidence of T.E.
25	Tromexan	53 W M	RSR	0	0	No response to treatment of failure. Prothrombin 10-20%. Died on 5th day. No autopsy. No clinical evidence of T.E.
26	Tromexan	84 W M	RSR	0	+	No response to treatment of failure. Prothrombin 30-40%. Patient developed uremia and died on 7th day. No autopsy. No clinical evidence of T.E.
27	Tromexan	79 W M	RSR	0	0	Little response to treatment of failure. Prothrombin 10-20%. Sudden dyspnea and chest pain, died on 5th day. No autopsy.
28	Tromexan	73 W M	RSR	0	0	Poor response to treatment of failure. Prothrombin 20-30%. Developed uremia and died on 8th day. No autopsy. No clinical evidence of T.E.
29	Tromexan	67 W M	RSR	0	+	No response to treatment of failure. Prothrombin less than 10%. Died on 4th day. No autopsy. No clinical evidence of T.E.
30	Tromexan	65 W F	AF	0	+	No response to treatment of failure. Prothrombin less than 10%. Died on 5th day. No autopsy. No clinical evidence of T.E.

*Coronary Artery Disease without Hypertension*

1	Control	77 C M	RSR	0	0	Good response to treatment of failure. Embolus to left popliteal artery on 7th day. Leg amputated and patient died on 27th day. No autopsy.
2	Control	73 W F	RSR	0	0	Good response to treatment of failure. Developed precordial pain and went into shock on 6th day. Died on 7th day. No autopsy.
3	Control	79 W M	RSR	+	0	Little response to treatment of failure. Died on 15th day. No autopsy. No clinical evidence of T.E.
4	Control	75 W F	AF	+	+	Slow response to treatment of failure. Patient died on 7th day. Autopsy: congestive heart failure old myocardial infarct, no recent T.E.

TABLE III—Continued

No.	Group	Age Color Race	Rhythm	P.H.T.E.	Fail- ure	Comment
5	Control	79 W F	RSR	0	+	Good response to treatment of failure. On 3rd day patient passed tarry stool. On 8th day had hematemesis and died. Autopsy: bleeding duodenal ulcer, no T.E.
6	Control	75 W M	RSR	0	+	Fair response to treatment of failure. Suddenly died on 16th day. No autopsy.
7	Control	59 W M	AF	+	+	Good response to treatment of failure. Sudden onset of chest pain and cough on 6th day. Died on 7th day. Autopsy: pulmonary embolus.
8	Control	47 W M	AF	0	+	Good response to treatment of failure. Conversion to regular rhythm attempted. On 12th day sudden chest pain and hemoptysis. X-ray showed pulmonary infarct. Patient recovered.
9	Control	60 W M	RSR	0	0	Poor response to treatment of failure. Died on 4th day. No autopsy. No clinical evidence of T.E.
10	Control	56 W M	RSR	0	+	Good response to treatment of failure. Thrombophlebitis noted on 9th day. On 10th day chest pain and pulmonary infarct demonstrated on x-ray. Anticoagulants started and patient recovered.
11	Control	75 W M	AF	0	+	Good response to treatment of failure. Died suddenly on 8th day. Autopsy: acute myocardial infarct.
12	Depo-Heparin	60 W M	RSR	0	+	Slow response to treatment of failure. Adequate anticoagulant therapy. Intermittent episodes of chest pain and cough. Died on 5th day. Autopsy: pulmonary infarcts.
13	Depo-Heparin	72 W M	AF	+	+	No response to treatment of failure. Adequate anticoagulant therapy. Died on 11th day. No autopsy. No clinical evidence of T.E.
14	Depo-Heparin	85 W F	RSR	0	0	Poor response to treatment of failure. Adequate anticoagulant therapy. Clotting time not unduly prolonged. Sudden coma on 8th day and died on 9th day. Autopsy: intracerebral hemorrhage. No evidence of hemorrhage elsewhere. No T.E.
15	Dicumarol and Heparin	61 W M	AF	0	+	No response to treatment of failure. Prothrombin less than 10%. Died on 7th day. No autopsy. No clinical evidence of T.E.
16	Dicumarol and Heparin	68 W M	AF	+	+	Good response to treatment of failure. Prothrombin 10-20%. CVA on 11th day. Died on 12th day. No evidence of hemorrhage. No autopsy.
17	Dicumarol and Heparin	82 W F	AF	+	0	Good response to treatment of failure. Prothrombin less than 10%. Passed a tarry stool on 7th day. 200 mg. emulsified vitamin K <sub>1</sub> given intravenously. Prothrombin rose to 69% in 12 hours. No further evidence of bleeding. Patient was out of failure and anticoagulants were not reinstituted. Patient died during night of 8th day. No autopsy. No clinical evidence of T.E.

TABLE III—Continued

No.	Group	Age Color Race	Rhythm	P.H.T.E.	Fail- ure	Comment
18	Dicumarol and Depo- Heparin	67 W F	AF	0	+	No response to treatment of failure. Prothrombin less than 10%. Died on 20th day. Autopsy: congestive heart failure, no T.E.
<i>Hypertensive Heart Disease with Coronary Artery Disease</i>						
*	Control	79 W M	RSR	+	0	Fair response to treatment of failure. CVA on 7th day and died on 9th day. No autopsy.
2	Control	68 W M	AF	0	+	Good response to treatment of failure. Chest pain and EKG changes of anterior myocardial infarction on 8th day. No autopsy.
3	Control	70 W M	AF	0	0	Good response to treatment of failure. Suddenly died on 16th day. No autopsy.
4	Control	67 W M	AF	+	+	Fair response to treatment of failure. Developed hemiplegia and died on 8th day. No autopsy.
5	Control	67 W F	RSR	0	0	No response to treatment of failure. Developed severe chest pain on 3rd day and died on 5th day. Autopsy: acute myocardial infarct.
6	Control	69 C F	RSR	+	+	Good response to treatment of failure. Suddenly died on 11th day. Autopsy: acute myocardial infarct.
7	Control	86 W F	RSR	0	+	No response to treatment of failure. Developed an intestinal obstruction and died on 7th day. No autopsy. No clinical evidence of T.E.
8	Dicumarol	42 W F	AF	0	0	No response to treatment of failure. Prothrombin 20-30%. Died on 7th day. No autopsy. No clinical evidence of T.E.
9	Dicumarol	73 W M	AF	+	+	Poor response to treatment of failure. Prothrombin 20-30%. Died on 6th day. Autopsy: congestive heart failure, no T.E.
10	Depo-Heparin	83 W F	AF	0	0	Slow response to treatment of failure. Adequate anticoagulant therapy. Developed bronchopneumonia and died on 9th day. No autopsy. No clinical T.E.
<i>Miscellaneous Heart Diseases</i>						
1	Control Luetic	55 W F	RSR	0	+	Poor response to treatment of failure. Died on 36th day. Autopsy: congestive heart failure, no T.E.
2	Control, Cor pulmonale	76 W F	RSR	0	0	Poor response to treatment of failure. Chronic asthma and severe anoxemia. Died on 8th day. No autopsy. No clinical evidence of T.E.
3	Control, Cor pulmonale	58 W F	RSR	0	+	No response to treatment of failure. Died on 13th day. No autopsy. No clinical T.E.
4	Depo-Heparin Cor pulmo- nale	60 W M	RSR	0	0	No response to treatment of failure. Adequate anticoagulant therapy. Died on 8th day. Autopsy: congestive heart failure, bronchopneumonia, no T.E.
5	Tromexan, Cor pulmonale	71 W M	RSR	0	+	No response to treatment of failure. Prothrombin 10-20%. Died on 7th day. No autopsy. No clinical evidence of T.E.

TABLE IV  
Patients with Maintenance Prothrombin Above 60 Per Cent  
*Dicumarol*

No.	Diagnosis	Age Race Sex	Rhythm	P.H.T.E.	Failure	Comment
1	HHD	65 W F	RSR	0	+	Good response to treatment of failure. One dose of Dicumarol given. Prothrombin level fell to 65%, thereafter rose to 86%. Discharged on 11th day.
2	HHD	73 W M	AF	+	+	Good response to treatment of failure. Prothrombin fell to 40% on 3rd day. Subsequently rose above 60%. Discharged on 7th day.
3	ASHD	87 W F	AF	0	+	Fair response to treatment of failure. Received Dicumarol for 3 days. Prothrombin fell to 65%. Suddenly died on 4th day. No autopsy.
4	ASHD	72 W M	RSR	+	0	Good response to treatment of failure. Prothrombin fell to 54% on 4th day. Subsequently above 60%. Discharged on 8th day.
5	ASHD	70 W F	AF	0	0	Minimal response to treatment of failure. Prothrombin fell to 62% on 4th day when discharged against medical advice.
6	ASHD	75 W F	AF	0	+	Good response to treatment of failure. One dose of Dicumarol given. Prothrombin fell to 50% on 3rd day. Subsequently rose above 60%. Discharged on 9th day.
7	Luetic	67 W M	RSR	0	+	Good response to treatment of failure. Prothrombin fell to 48% on 3rd day. Subsequently rose above 60%. Discharged on 8th day.

*Depo-Heparin and Dicumarol*

1	RHD	33 W F	AF	0	+	Slow response to treatment of failure. Prothrombin fell to 30% on 3rd day and no further Depo-Heparin given. Subsequently prothrombin rose above 60%. On 13th day prothrombin 90% and patient had chest pain and x-ray evidence of pulmonary infarction. Subsequently patient treated satisfactorily with anticoagulants and discharged on 23rd day.
2	RHD	52 W M	RSR	+	+	Good response to treatment of failure. Prothrombin fell to 53% on 3rd day. Developed ecchymosis at site of Depo-Heparin injections. Anticoagulants were discontinued. Prothrombin rose above 60%. Discharged on 7th day.
3	HASHD	61 W M	AF	+	+	Good response to treatment of failure. Prothrombin fell to 40% on 4th day. Anticoagulants discontinued because of uremia. Died on 8th day. Prothrombin 92%. No autopsy. No clinical evidence of T.E.
4	HASHD	65 C M	RSR	0	+	Good response to treatment of failure. Prothrombin fell to 40% on 3rd day. Hematoma developed at site of Depo-Heparin injection and anticoagulants were discontinued. Prothrombin rose above 60%. Discharged on 10th day.



TABLE IV—Continued

No	Diagnosis	Age Race Sex	Rhythm	P.H.T.E.	Failure	Comment
<i>Sodium Heparin and Dicumarol</i>						
1	RHD	61 W F	RSR	+	+	Slow response to treatment of failure. Prothrombin fell to 20% on 4th day. No further Heparin given, although prothrombin rose above 60%. Discharged on 15th day.
2	HHD	68 W M	AF	+	0	Slow response to treatment of failure. Prothrombin fell to less than 10% on 5th day. Subsequently rose above 60%. No further Heparin given. Discharged on 17th day.
<i>Tromexan</i>						
1	RHD	38 W M	AF	0	+	Slow response to treatment of failure. Prothrombin never fell below 60%. Died suddenly on 7th day. Autopsy: massive pulmonary embolus.
2	RHD	46 W M	AF	0	+	Fair response to treatment of failure. Prothrombin fell to 30% on 2nd day, but on 3rd day rose to 62%. Discharged against medical advice on 4th day.
3	RHD	47 W F	RSR	0	0	Good response to treatment of failure. Prothrombin fell to 32% on 3rd day but rose above 60% on 4th day. Discharged on 8th day.
4	RHD	52 W F	AF	+	+	Good response to treatment of failure. Prothrombin fell to 35% on 3rd day. Subsequently rose above 60%. Discharged on 8th day.
5	HHD	76 W F	RSR	0	+	Good response to treatment of failure. Prothrombin fell to 35% on 2nd day. Prothrombin rose to 70% on 3rd day. On 6th day had CVA, prothrombin 58% and died on 7th day. No autopsy.
6	HHD	78 W F	AF	0	+	Good response to treatment of failure. Prothrombin fell to 22% on 2nd day and rose to 64% on 3rd day, discharged on 6th day.
7	HHD	72 W M	RSR	+	0	Good response to treatment of failure. Prothrombin fell to 36% on 3rd day, subsequently rose to 60%, discharged on 7th day.
8	HHD	63 W F	AF	0	+	Good response to treatment of failure. Prothrombin fell to 40% on 5th day. Subsequently rose above 60%. Discharged on 12th day.
9	ASHD	86 W M	AF	0	0	Good response to treatment of failure. Prothrombin fell to 30% on 2nd day. Subsequently rose above 60%. Discharged on 10th day.
10	ASHD	72 W M	RSR	+	+	Good response to treatment of failure. Prothrombin fell to 26% on 3rd day. Subsequently rose above 60%. Discharged on 10th day.
11	HASHD	59 W M	RSR	+	0	Good response to treatment of failure. Prothrombin fell to 46% on 3rd day. Subsequently on 4th day rose to 67%. Discharged on 5th day.

TABLE IV—Continued

No.	Diagnosis	Age Race Sex	Rhythm	P.H.T.E.	Fail- ure	Comment
12	HASHD	50 C M	RSR	0	0	Poor response to treatment of failure. Gradual downward course. One dose of Tromexan given. Prothrombin fell to 40% on 3rd day, but was up to 80% on 4th day. Patient died on 8th day. No autopsy. No clinical evidence of T.E.
13	HASHD	56 W M	RSR	0	0	Good response to treatment of failure. Prothrombin fell to 40% on 2nd day. Subsequently rose above 60%. Discharged on 5th day.

In the treated patients, a statistically significant reduction in thromboemboli was evident in all types of heart disease except in the miscellaneous group, where no thromboemboli were observed in either the control or treated patients. Seven thromboemboli were observed in the treated group as a whole, an incidence of 1.8 per cent. Thirty-three thromboemboli were observed in the control group, an incidence of 15.5 per cent.

An attempt was made to determine the critical level of hypoprothrombinemia necessary for satisfactory prophylaxis of patients treated with the coumarin anticoagulants. Twenty-six patients have been excluded from the study in the previous data presented. These were patients in whom the maintenance prothrombin level was above 60 per cent. Brief summaries of these patients appear in table 4. The composition of this group was essentially the same as that of the control group. A 23 per cent mortality and 15.4 per cent incidence of thromboemboli are noted. These are almost identical to the values found in the control patients.

Table 5 shows the number of patients and number of thromboemboli at various maintenance levels of hypoprothrombinemia. A statistically significant decrease in thromboemboli is observed in those patients maintained below 60 per cent, as compared to the group whose maintenance level was greater than 60 per cent. Only 1.8 per cent of the patients whose maintenance prothrombin level was below 60 per cent had thromboemboli, whereas 15.4 per cent of the patients maintained above 60 per cent had thromboemboli and 15.5 per cent of the control series experienced thromboemboli.

TABLE V

Prothrombin Level	Treated Patients					Control
	Less 10-20%	21-40%	41-60%	Total under 60%	Over 60%	
Thromboemboli	2	2	1	5	4	33
Total Patients	70	165	36	271	26	213

TABLE VI  
Hemorrhagic Phenomena

Control						
No.	Diagnosis	Age Race Sex	Rhythm	P.H.T.E.	Fail- ure	Comment
1	RHD	41 C F	RSR	0	0	Good response to treatment of failure. On 11th day sudden hematemesis, melena and died. No autopsy.
2	RHD	52 W M	AF	0	+	Good response to treatment of failure. On 8th day passed tarry stool. X-ray showed duodenal ulcer.
3	HHD	66 W F	RSR	0	+	Fair response to treatment of failure. Sudden coma and died on 4th day. Autopsy: extensive cerebral hemorrhage, no T.E.
4	HHD	55 W M	AF	0	+	Good response to treatment of failure. On 3rd and 7th days moderate epistaxis. No other bleeding. Discharged on 10th day.
5	ASHD	79 W F	RSR	0	+	Good response to treatment of failure. On 3rd day patient passed tarry stool. On 8th day had hematemesis and died. Autopsy: bleeding duodenal ulcer. No T.E.
6	ASHD	62 W F	RSR	0	0	Good response to treatment of failure. On 5th day went into shock and passed bloody stool. Responded to transfusion. Carcinoma of the sigmoid was demonstrated.
Dicumarol						
1	RHD	38 W M	AF	0	+	Good response to treatment of failure. On 4th day epistaxis, prothrombin less than 10%. Fifth day, prothrombin 12%—no further bleeding. Discharged on 8th day.
2	HHD	71 W F	RSR	0	+	Good response to treatment of failure. On 8th day prothrombin less than 10% and patient had a massive hematemesis. Given 100 mg. emulsified vitamin K <sub>1</sub> intravenously and 500 c.c. of blood. Patient responded but 8 hours later suddenly became cyanotic and died. Not classed as T.E.
3	HHD	59 W F	RSR	0	0	Good response to treatment of failure. Epistaxis on 4th day when prothrombin less than 10%. This ceased spontaneously, although anticoagulants were continued. Prothrombin maintained between 10–20%. Discharged on 10th day.
4	HHD	72 W M	AF	+	0	Good response to treatment of failure. On 4th day patient developed gross hematuria. Prothrombin was less than 10%. Hematuria continued for 3 days despite Synkavite administration. No cause for G.U. bleeding found. Discharged on 12th day.
Depo-Heparin						
1	RHD	42 W M	RSR	0	0	Good response to treatment of failure. Epistaxis on 3rd day, at which time clotting time was 36 minutes. No further bleeding occurred, although anticoagulant was continued. Discharged on 9th day.

TABLE VI—Continued

No.	Diagnosis	Age Race Sex	Rhythm	P.H.T.E.	Failure	Comment
2	HHD	71 W M	RSR	0	+	Slow response to treatment of failure. Adequate anticoagulant therapy. Clotting time not unduly prolonged. Sudden coma and died on 8th day. Autopsy: intracranial hemorrhage, no other hemorrhage found, no T.E.
3	HHD	76 W F	RSR	0	0	Good response to treatment of failure. On 7th day multiple ecchymoses appeared. Clotting time 120 minutes. Patient was out of failure and anticoagulant was discontinued. Discharged on 12th day. No further hemorrhage.
<i>Depo-Heparin and Dicumarol</i>						
1	RHD	52 W M	RSR	+	+	Good response to treatment of failure. Prothrombin fell to 53% on 3rd day. Developed ecchymosis at the site of Depo-Heparin injections. Anticoagulants were discontinued. Prothrombin rose above 60%. Discharged on 7th day.
2	HASHD	65 C M	RSR	0	+	Good response to treatment of failure. Prothrombin fell to 40% on 3rd day. Hematoma developed at site of Depo-Heparin injection and anticoagulants were discontinued. Prothrombin rose to above 60%. Discharged on 10th day.
<i>Sodium Heparin and Dicumarol</i>						
1	ASHD	82 W F	AF	+	0	Good response to treatment of failure. Prothrombin less than 10%. Passed a tarry stool on 7th day. 200 mg. of emulsified vitamin K <sub>1</sub> given intravenously and prothrombin rose to 60% in 12 hours. No further evidence of bleeding. Patient was out of failure and anticoagulants were not reinstituted. Patient died during night of 8th day. No autopsy. No clinical evidence of T.E.
2	ASHD	59 C M	AF	0	+	Good response to treatment of failure. Developed ecchymosis over site of Heparin injection. Dicumarol was continued and no further bleeding encountered. Discharged on 10th day.
<i>Tromexan</i>						
1	HASHD	63 W M	RSR	0	+	Good response to treatment of failure. On 5th day prothrombin less than 10%. Patient passed tarry stool. 300 mg. of emulsified vitamin K <sub>1</sub> given intravenously. Prothrombin rose to 97% in 16 hours. Patient was out of failure and anticoagulants were discontinued. No cause for bleeding found. Discharged on 12th day.

Table 6 summarizes the histories of those patients in the control and treated groups who had major or minor hemorrhagic phenomena. An incidence of 2.8 per cent was observed in the control group and 2.9 per cent in the treated group. Five of the control group had major hemorrhage and five of the treated patients had major hemorrhage. In the patients treated with Dicumarol or Tromexan, in no instance was hemorrhage noted when the prothrombin level was above 10 per cent.

#### DISCUSSION

The benefit which adjuvant anticoagulant therapy offers patients hospitalized with congestive heart failure is substantiated by the results of this study. A significant reduction in fatality rate was observed in patients with rheumatic heart disease (over 40 years of age) and in coronary artery disease without hypertension. A significant reduction in thromboemboli was found in heart disease of all etiologies studied except cor pulmonale and luetic heart disease.

Cardiac arrhythmia, a past history of congestive heart failure or a past history of thromboemboli was not found to influence the outcome in either the treated or the control series. This is very interesting and implies an equal vulnerability of all patients hospitalized with congestive heart failure, irrespective of past history or cardiac rhythm.

The various anticoagulants studied appeared to be equally beneficial. The advantage of rapid reversibility of hypoprothrombinemia found with Tromexan is a definite safety factor. Some difficulty was encountered in maintaining stable levels of hypoprothrombinemia with this agent. This was ascribed to the rapidity of change in prothrombin level and to the dependence of response to a given dose upon whether the prothrombin level was rising or falling at the time the dose was given. To overcome this difficulty it was found necessary to give the Tromexan in a divided dose and to make twice daily determinations of the prothrombin level.

A striking reduction in the incidence of thromboemboli was found in the patients treated with the coumarin anticoagulants who were maintained with prothrombin levels of less than 60 per cent. Clinically it has been thought for some time by one of this group (G. C. G.) that in prophylactic anticoagulant therapy it is not necessary to maintain patients at near-hemorrhagic levels. Brambel<sup>11</sup> has noted that protection appears to be offered when coumarin anticoagulants are used prophylactically, if the prothrombin level is maintained at 40 to 50 per cent. In the present series, the number of patients whose prothrombin levels were between 40 and 60 per cent was not sufficiently large to demonstrate significantly poorer results than obtained with levels under 40 per cent. It is thought at this time that the upper limit of safety for prophylactic anticoagulant therapy may be approximately 45 per cent.

It should be made clear that this level applies to patients who are being

given purely prophylactic anticoagulant therapy. When active intravascular clotting has begun, it is probably necessary to depress the prothrombin level to 10 to 20 per cent of normal. If it is true that protection against thromboemboli is offered by levels up to 45 per cent, then some of the problems in the management of Tromexan will not be so serious, and the rapid induction and disappearance of hypoprothrombinemia with this drug may be advantageous.

The problem of hemorrhage during anticoagulant therapy is a very real one. When one gives an anticoagulant there is a calculated risk of producing hemorrhage due to excessive depression of the normal hemostatic mechanisms. However, hemorrhage can and does occur in patients not receiving anticoagulants. In the patients observed by the Committee for the Evaluation of Anticoagulants in the Treatment of Myocardial Infarction of the American Heart Association,<sup>12</sup> 6 per cent of the control patients had hemorrhagic phenomena. In their treated patients, 12.4 per cent had hemorrhagic phenomena. It was noted that approximately one-half of these were not due to anticoagulants. Nichol<sup>13</sup> has reported a 2 per cent incidence of major hemorrhage and a 4 per cent incidence of minor hemorrhage in approximately 15,500 patients. In the present report the control group showed a 2.8 per cent incidence of hemorrhage, with five cases of major hemorrhage, and the treated patients had a 2.9 per cent incidence of hemorrhage, with five cases of major hemorrhage.

At no time during this study was hemorrhage encountered with the coumarin drugs when the prothrombin level was above 10 per cent. This is in contrast to the reports of some authors,<sup>14</sup> who claim that hemorrhage has occurred at considerably higher prothrombin levels. Since hemorrhage can occur even without anticoagulants, it may be that some of the patients reported as hemorrhaging with prothrombins above 10 to 20 per cent would have bled irrespective of anticoagulant therapy. It is also possible that the method of prothrombin estimation used resulted in erroneous values.<sup>15</sup>

Fortunately, bleeding from heparin drugs can be easily controlled with intravenous protamine and application of ice bags at the site of heparin injection. Recent reports of rapid reversal of coumarin induced hypoprothrombinemia with intravenous emulsified vitamin K<sub>1</sub>\* have been encouraging.<sup>16</sup> In the few patients in this series receiving this form of vitamin K<sub>1</sub> the results have been excellent. It does not seem that fear of hemorrhage should be a deterrent to the use of anticoagulants prophylactically in congestive heart failure where their benefit so exceeds the minimal risk involved. This presumes, however, that dosage is properly controlled by laboratory tests.

During the second year of this study, a modification of Owren's prothrombin method has been found satisfactory for assessing the prothrombin level. With this method the only known variable affecting the length of

\* Emulsified Vitamin K<sub>1</sub>, kindly supplied by Merck & Co., Inc., Rahway, New Jersey.



time for fibrin clot formation is the prothrombin content. This method offers a number of theoretic and practical advantages over the one-stage method of Quick. Briefly, the following variables are removed or controlled. First, the plasma is diluted 10 times, which eliminates the effect of heparin, antithrombin and antithromboplastin. This dilution also minimizes changes in oxalate or citrate concentration in the unknown plasma resultant from hematocrit variation. Second, a constant quantity of accelerator globulin, fibrinogen and oxalate are added in an aliquot of oxalated prothrombin-free beef plasma. This eliminates changes in these factors which may occur in the unknown plasma and markedly affect and falsify the results of the regular Quick procedure. Third, measuring the prothrombin converting ability of the thromboplastin on serially diluted stable prothrombin standards eliminates the variability of this reagent.

Over the past two years this method has been used routinely at the Los Angeles County Hospital. It has been found, in agreement with Owren<sup>17</sup> and Astrup,<sup>18</sup> to be ideally suited for the control of coumarin therapy.

#### SUMMARY

1. The results of anticoagulant therapy in 416 of 627 patients with congestive heart failure are presented.
2. Statistically significant reduction in thromboembolism was observed in 390 patients maintained at prothrombin levels below 60 per cent.
3. Cardiac arrhythmia, a past history of congestive heart failure or a past history of thromboemboli was not found to influence the outcome in either the treated or the control series.
4. It is suggested that adequate prophylaxis may be obtained with prothrombin levels up to 45 per cent.
5. The anticoagulants Depo-Heparin, Dicumarol, Tromexan, and Dicumarol with either Depo-Heparin or Sodium Heparin were equally beneficial.
6. Some problems relative to the administration of Tromexan are discussed.
7. Hemorrhagic phenomena were observed in 2.8 per cent of the control group and in 2.9 per cent of the treated series. Fear of hemorrhage should not be a deterrent to judicious prophylactic anticoagulant therapy.
8. A new method for determining prothrombin has been satisfactorily used to control dosage of the coumarin drugs.
9. The consensus among the 30 residents and the investigators is that the addition of anticoagulant therapy to the conventional treatment of congestive failure is beneficial, but is to be undertaken only under strict clinical observation and an adequate, dependable anticoagulant laboratory.

#### ACKNOWLEDGMENT

The technical assistance of Mary Troutman, B.A., and Frank B. Cramer, B.S., and the cooperation of the regular hospital staff of the Los Angeles County Hospital are gratefully acknowledged.



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## CONGENITAL INTERATRIAL COMMUNICATIONS: CLINICAL AND SURGICAL CONSIDERATIONS WITH A DESCRIPTION OF A NEW SUR- GICAL TECHNIC: ATRIO-SEPTO-PEXY \*

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DEVELOPMENTAL defects of the interatrial septum which allow a shunt of blood between the chambers are of frequent occurrence. This abnormality, alone or in combination with other cardiac or great vessel malformations, accounts for a large proportion of any series of congenital cardiac defects.

Although a few patients with relatively large atrial septal defects live to old age with surprisingly little evidence of cardiac embarrassment, the majority of such individuals are not so fortunate. For that reason our interest has been turned to the possibility of surgical therapy. The present communication reports our efforts along that line and reviews the current knowledge of the condition.

### EMBRYOLOGY

Between the fourth and fifth fetal weeks, when the human embryo is about 6 mm. in size, the primitive atrial chamber which, with the sinus venosus, the single ventricle and the bulbus cordis, has composed the heart, is divided by a thin crescentic membrane growing down from the mid-dorsal wall. This is the *septum primum*. Meanwhile, the atrioventricular canal connecting the common atrium and common ventricle is being divided. Two cushions of endocardial tissue, one growing from the dorsal and the other from the ventral wall of the canal, fuse and thus a right and a left atrioventricular canal are formed, the sites of the future tricuspid and mitral valves. As the *septum primum* develops it finally meets and fuses with the endocardial cushions; thus, separate right and left atrial chambers come into existence. As the *septum primum* is completed, however, there develops in its upper portion a new opening between these cavities, the *foramen secundum*. This, at first, is an affair of multiple perforations. It soon loses its lacework character and a single aperture develops. In the seventh fetal week another septum, the *septum secundum*, develops to the right of

\* Presented at the Thirty-third Annual Session of the American College of Physicians, Cleveland, Ohio, April 21, 1952.

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the septum primum and grows down in crescentic fashion to separate the atria again except for an area in the posterosuperior region, the *foramen ovale*. The septum primum and septum secundum become fused except for a portion of the septum primum, which forms a valvelike flap over the foramen ovale. The atrial septum is now fully formed, and during the remainder of fetal life blood must pass through the foramen ovale to the left heart. As the flap over this orifice is on the left atrial aspect of the septum, the flow from the right atrium is free. Following birth the foramen ovale becomes functionally closed, the time varying between wide limits. In most cases, anatomic closure as a result of fusion of the valve to the septum secundum follows within a matter of months.<sup>1</sup>

Disruption of the developmental process at any point may result in a communication between the two atria which will persist beyond fetal life.

#### PATHOLOGY

The most commonly encountered interatrial communication is a patent foramen ovale. It usually is not considered a congenital defect because it merely represents failure of the septum primum and septum secundum to complete their fusion when patency is no longer necessary. However, since it indicates a halt in the development of the definitive septum, it should be considered a malformation. The size of the persistently patent foramen varies. It may admit only a fine probe or, depending on the factor of atrial pressure, may be very large.

Failure of the septum primum to meet and to fuse with the endocardial cushions results in a defect just above the tricuspid and mitral valves, the persistent ostium primum. Absence of the inferior portion of the septum primum and of the membranous portion of the interventricular septum results in the condition known as *atrioventricularis communis*. The tricuspid and mitral valves are fused; when they are open, there exists continuity of all four cardiac chambers. The cusps of these valves may be anomalous.

Absence of the septum secundum allows persistent communication through the defect which developed in the upper portion of the septum primum, the foramen secundum.

Finally, there may be complete absence of the atrial septum, as in *cor biloculare* and *cor triloculare (biventriculare)*, or localized small defects, single or multiple, in any area.

Certain associated abnormalities which are frequently present give rise to more or less distinctive clinical pictures: pulmonary stenosis, aberrant drainage of pulmonary veins into the right atrium or venae cavae, mitral stenosis, tricuspid atresia, transposition of the great vessels, Ebstein's malformation of the tricuspid valve.

A tabular classification of these various malformations is given in table 1.

TABLE I  
Atrial Septal Communications

- I. Uncomplicated
  - A. Patent foramen ovale. No shunt.
  - B. Complete absence of septum. Shunt in both directions due to mixing.
  - C. Persistent ostium primum. Left-to-right shunt.
  - D. Persistent ostium secundum. Left-to-right shunt.
  - E. Localized single or multiple defects at any point in septum. Left-to-right shunt.
- II. Complicated
  - A. Atrioventricularis communis. Predominant left-to-right shunt.
  - B. Patent foramen ovale with
    1. Pulmonary stenosis. Right-to-left shunt.
    2. Mitral stenosis. Left-to-right shunt.
    3. Ebstein's malformation of the tricuspid valve. Right-to-left shunt.
    4. Anomalous pulmonary vein drainage, complete, into right atrium or venae cavae. Right-to-left shunt.
  - C. Atrial septal defect (I-C, D or E) with
    1. Pulmonary stenosis. Right-to-left shunt.
    2. Mitral stenosis. Left-to-right shunt.
    3. Ebstein's malformation. Right-to-left shunt.
    4. Tricuspid atresia. Right-to-left shunt.
    5. Transposition of the great vessels. Shunt bi-directional.

#### PATHOLOGIC PHYSIOLOGY

Blood flow through atrial communications depends upon a number of factors: size of opening, relative pressures in right and left atria and associated lesions, congenital or acquired.

Flow through the foramen ovale with only probe patency probably does not occur in an otherwise normal heart. It has been shown that the pressure in the left atrium is normally greater than that in the right. Inasmuch as the valve of the foramen ovale is actually the superior portion of the definitive septum primum and opens to the left, the increased pressure would serve to keep it plastered over the foramen and to prevent blood flow. If for any reason pressure is raised above physiologic limits in either right or left atrium, the relationship of valve to septum may change. If pressure in the right chamber becomes predominant, the valve is forced open and a right-to-left shunt becomes possible. With continued rise in pressure, the right atrium dilates. Then there is a tendency to pull the lips of the foramen further apart and to make it impossible for the valve to function. The right-to-left shunt becomes greater in proportion to the increasing size of the opening and to the increasing pressure. Similarly, if left atrial pressure rises to a height which will cause dilatation of that chamber, the septum may become stretched; the valve becomes incompetent and a left-to-right shunt is allowed.

Thus, in the presence of pulmonary stenosis with an intact ventricular septum, a right-to-left shunt through a patent foramen ovale becomes possible (a) after the right ventricle has dilated to the point where functional tricuspid insufficiency develops, or (b) because blood "piles up" in the right atrium when its companion chamber is unable to accept more. In each instance, right atrial pressure increases to the point where a gradient exists

from right to left. Cyanosis then may become apparent. This shunt allowed by the patent foramen ovale may be regarded as sparing of the heart, for it serves to limit somewhat rises in right heart pressure. This has been shown experimentally.<sup>3</sup>

Likewise, in Ebstein's malformation of the tricuspid valve, in which patency of the foramen ovale is frequently encountered, there is a tendency for blood to "pile up" in the right atrium. A right-to-left shunt develops by the same mechanism as that described above.

In the presence of mitral stenosis, on the other hand, interference with left atrial output causes a rise in pressure in that chamber. Dilatation results in stretching of the septum and brings about incompetency of the foramen ovale valve. A left-to-right shunt ensues.

It can be appreciated that, in the three conditions discussed, an actual septal defect will function in the same manner as the patent foramen ovale.

In instances of actual localized absence of septal tissue without other malformations, a number of explanations to account for the cause and direction of interatrial flow have been offered. Wiggers' <sup>2</sup> demonstration of higher pressure in the left than in the right atrium of dogs pointed to an obvious mechanism of left-to-right flow. Uhley <sup>4</sup> suggested that, since the left atrium is above the right and the septum lies in the horizontal plane, gravity would affect interatrial flow. He found in this thesis the explanation for the infrequency of symptoms in infants with the lesion: most of the early months of life are spent in the recumbent position, and the gravitational force is not in effect. With assumption of upright posture, however, gravitational flow becomes certain, and a left-to-right shunt results. Brannon, Weens and Warren <sup>5</sup> tested his concept in patients with atrial septal defect demonstrated by cardiac catheterization. They reasoned that if the relative positions of the atria were so important a factor, reversing their spatial relationship would favor a flow from right-to-left. Such a shunt would express itself in a lowering of peripheral arterial oxygen saturation. This effect could not be accomplished. Dexter <sup>6</sup> and his associates, by means of cardiac catheterization in a patient with atrial septal defect, discovered left atrial pressure to be 10 mm. Hg, while that of the right was only 6 mm. This gradient would naturally favor a left-to-right flow. Courmand and his coworkers <sup>7</sup> succeeded in obtaining left atrial pressure tracings in three patients. They too found a gradient of pressure which would allow a left-to-right shunt. They pointed out, in addition, that a reversal of flow (right-to-left) was possible during a short phase of the cardiac cycle, on the basis of a lower level of pressure in the left atrium during the period corresponding to the descent of the base. To explain the higher left atrial pressure, they point to two anatomic differences between the two atria: the left atrial wall is thicker than the right, and the reservoirs of the left (pulmonary veins) are smaller than those of the right (*venae cavae*). These differences suggest the left atrium to be less distensible than the right and the capacity of its reservoirs to be less. In addition, the

musculature of the left ventricle being thicker than that of its opposite, the effects of activity of this chamber on the volume and tension of the left atrium may be more pronounced than the activity of the right ventricle on right atrial blood. Barger, Edwards, Parker and Dry<sup>9</sup> believed that, in all probability, the factor principally responsible for the left-to-right shunt is the relative resistance to filling of the right and left ventricles, that of the left being greater than that of the right. Hull<sup>8</sup> concluded that the direction of interatrial shunts is due to differences in the normal anatomic features of the mitral and tricuspid valves and of the right and left ventricles. These differences (smaller mitral orifice, longer and narrower left ventricle, less efficient mitral valve) are responsible for greater resistance to emptying of the left atrium, with consequent higher left atrial pressure during ventricular diastole, allowing a left-to-right shunt through a septal defect. In the presence of experimentally produced atrial septal defects in dogs, Little, Opdyke and Hawley<sup>10</sup> showed that the pressure differential existing between the left and right atria depends on the lesser distensibility of the left atrium and the increase in right ventricular output. In a subsequent paper<sup>11</sup> from the same laboratory, changes in intrathoracic pressure were reported to modify and reverse the direction of the pressure gradient, and it was concluded that respiratogenic changes in interatrial pressure gradient offer one explanation for the varying direction of blood shunt in some patients with atrial septal defect. Hickam,<sup>12</sup> from data derived from four patients with atrial septal defect in whom the catheter entered a pulmonary vein, concluded that the dynamics of hearts with atrial septal defects are not determined simply by atrial pressure levels, having found that the values of the intracardiac shunts can change spontaneously and with exercise. During exercise, changes in right and left ventricular output were not parallel, and in two cases changes in right ventricular output were opposite in direction to changes in right atrial pressure.

Whatever its exact mechanism, the predominating shunt in uncomplicated defects is left-to-right. There is increased filling of the right ventricle and, in consequence, increased pulmonary flow. The right atrium must dilate to accommodate the burden of extra blood; a degree of hypertrophy ultimately appears. The right ventricle must accept the added blood and expel it; dilatation and hypertrophy result. The pulmonary arterial system in turn dilates. The left heart, on the other hand, receives little impetus for change. The left atrium, in spite of receiving a large volume of recirculated blood, retains its normal size or dilates but little, since it is furnished with the escape valve of the defect. The left ventricle, because it receives little of the recirculated blood, remains normal in size. The oft-described hypoplasia of the aorta has been explained on the basis of decreased flow through the left ventricle. Actually, since so many patients compensate well for the defect, it follows that left ventricular output is maintained and hence aortic flow is normal or near normal. It would seem reasonable to assume that this aortic "hypoplasia" is, in most cases, more apparent than



real, the vessel appearing abnormally small in relation to the very large pulmonary artery. It may be mentioned that one explanation for the clinical and pathologic features of atrial septal defect supposes it to be merely a single feature of a complex congenital deformity involving a dilated right atrium, right ventricle and pulmonary artery, and hypoplasia of the left ventricle and aorta.<sup>12</sup> This is, at best, a theory which relieves one of the necessity of determining cause and effect.

Pulmonary hypertension developing during the natural history of atrial septal defect introduces a new element into the dynamics. It is impossible at present to state how frequently an appreciable rise in pulmonary arterial pressure occurs. Of Wood's<sup>14</sup> series of 25 cases who were catheterized, only one had a mean pulmonary artery pressure over 18 mm. Hg. In the relatively few cases reported by others for whom data are given, a mean pulmonary artery pressure of 25 mm. Hg or over (systolic of 50 mm. or more) was found in approximately 39 per cent. In our own series, mean pulmonary artery pressure has been elevated in about 40 per cent of the cases. It is of course apparent that a normal pressure at only one point in a patient's course means little, and one cannot say that with the passage of time most individuals will not show a significant rise. We believe that pulmonary hypertension is probably present in all of those in whom severe symptoms develop.

Until the mechanism of the hypertension is more acceptably explained, one may attribute it to increased peripheral pulmonary resistance due to changes in the vessel walls which serve to decrease the size of the lumina, and to the increased flow itself. The cause of the pulmonary vascular changes is speculative. Increased blood flow is one obvious possibility. Perhaps the increased oxygen content of this blood plays a rôle. In line with Edwards' <sup>15</sup> explanation of the pulmonary changes in Eisenmenger's complex and other malformations in which there is an opportunity for increased pulmonary flow at the expense of systemic flow, one might attribute the changes in this condition to a protective response. By increasing peripheral pulmonary resistance, a decrease in the left-to-right shunt and a greater systemic flow ultimately result. Eventually this response itself negates its good because the hypertension places a terrible burden on the right heart.

Acceptance of pulmonary hypertension as a more-or-less characteristic development in the anomaly allows explanation of the cyanosis which appears in a number of these patients. The conclusion that frank cyanosis or a degree of arterial oxygen unsaturation is due to interference with oxygenation of blood at the pulmonary capillary level cannot longer be accepted. It has often been shown by catheterization of pulmonary veins through an atrial septal defect that oxygen uptake is normal. The reason for the decreased saturation is a right-to-left shunt at the atrial level. In cases with virtual absence of the septum, there may be a considerable degree of mixing of arterial and venous blood in what amounts to a common chamber,



with consequent lowering of the oxygen content of arterial blood. These cases are few, however, most defects being smaller. Selzer and Lewis<sup>18</sup> visualize a stream of blood thrown directly from one of the venae cavae into the left atrium during the part of the cycle when pressure differences between the atria are smallest, and causing no interference with the left-to-right shunt during the remainder of the cardiac cycle. Since such a mechanism would be caused by an anatomic chance (favorable relationship of one of the venae cavae to the septal opening), they feel that it would explain the occurrence of chronic cyanosis in the few patients in whom it is found. Actually, the inferior vena cava is in a suitable relationship to the atrial septal defect in a great many cases, as is evidenced by the frequency with which a catheter, with only the slightest curve at the tip, will pass into the left atrium when introduced through the saphenous or femoral vein. One would expect, then, to see cyanosis of a chronic nature in a large percentage of such cases. The reverse, however, is true.

We feel that the production of visible cyanosis follows the same pattern in uncomplicated defect that it does in atrial communication associated with pulmonary valvular stenosis or Ebstein's malformation: in each instance there is interference with free pulmonary flow. With rise in pulmonary artery pressure due to peripheral resistance, there is a consequent rise in right ventricular pressure. In the course of time, this chamber can no longer accept its burden. Right atrial emptying becomes inadequate because right ventricular emptying is incomplete. A gradual rise in right atrial pressure takes place. This serves to upset the left-to-right pressure gradient and there is a tendency to equalization. This will increase the volume of mixing in the area of the defect, and the right-to-left shunt, which perhaps heretofore was sufficient to cause only a minor degree of arterial oxygen unsaturation, is now great enough to produce visible cyanosis. This is possible without any clinical evidence of cardiac failure. In some patients this state of affairs may persist for a long time; in others, it is merely a terminal phenomenon.

#### THE CLINICAL PICTURE

*Incidence:* In the field of congenital heart disease, figures based on autopsy material mean but little. This applies particularly to Abbott's<sup>17</sup> series, so often cited in support of the rarity or frequency of a particular malformation. Likewise, the determination of incidence by clinical examination without such support as is furnished by cardiac catheterization, contrast roentgen study or surgical exploration is not acceptable. The actual incidence of atrial septal communications is unknown. Various post-mortem series of congenital cardiac malformations have shown it to comprise 2 to 24 per cent as the single lesion, and 33 to 40 per cent alone and in combination with other defects. The span of such figures attests to their unreliability. Too, many communications dismissed as being insignificant, and hence not mentioned, in the light of present day knowledge would be

stressed. In any event, there is no doubt that the incidence of atrial communications is high.

*Sex:* It has been remarked that atrial septal defect is more common in the female than the male. Roesler<sup>19</sup> collected 62 cases, accepting none in which the defect was under 1 cm. in diameter and no instances of single atrium. Thirty-seven (61.7 per cent) were female. Bedford, Papp and Parkinson<sup>18</sup> reported 53 observed cases, 10 of whom were autopsied. Of these, eight were female. Keith and Forsyth<sup>20</sup> found 11 of 14 cases proved by catheterization to be female. McGinn and White<sup>21</sup> reported a male with atrial septal defect associated with mitral stenosis. All but one of 23 previously reported cases had been females. Fifty-eight per cent of the proved cases in the series of Cosby and Griffith<sup>22</sup> were females. In Wood's<sup>14</sup> series of 35 cases, 25 of whom were catheterized, there were 12 males and 23 females. In our series of cases proved either by catheterization or autopsy, there has been a preponderance of females (60 per cent). Whether these figures can be regarded as significant remains for future determination, when large series from individual clinics can be considered.

*Physical Signs:* The habitus of patients with atrial septal defects has been referred to many times as characteristic: a frail stature with small bones and translucent skin. This is considered by Bedford, Papp and Parkinson<sup>18</sup> to be overrated. We agree, for in our patients this has not been a striking feature. Failure to gain well in early infancy, however, is not uncommon.

A precordial bulge is found in very many individuals but is not constant. It is no doubt due to pressure of an enlarging heart on the easily moulded ribs of the infant and young child, and is found in other malformations in which there is right heart dilatation and hypertrophy: tetralogy of Fallot, pulmonary stenosis, high interventricular septal defect, etc. Scoliosis occurs in some cases but is more common in patients with cyanotic lesions, such as the tetralogy of Fallot.

In patients severely affected, prominent cervical venous pulsations are present. By pressing the finger in the suprasternal notch a tracheal tug may be felt. This is due to an enlarged pulmonary artery pressing against the trachea and causing it to move with each systole.

Liver enlargement and tenderness are found in the presence of a failing heart. Pulsations of this organ are present with tricuspid incompetence in some individuals.

The cardiac findings are often striking but in some cases are of such nature as to escape detection by the careless examiner. As a rule the heart is enlarged, the point of maximal impulse being displaced outward and downward and the area of cardiac dullness increased to right and left. In children, physical examination may give no evidence of enlargement even though it is present. In our experience, a systolic thrill of maximal intensity in the second and third interspace is present in only about one-half of the patients. Disturbances of rhythm are not uncommon. Auricular fibrilla-

tion is of relatively frequent development, especially in those patients who have mitral stenosis. Premature systoles and paroxysmal tachycardia are often encountered. Extreme respiratogenic variations in rhythm have been seen in a few of our younger patients. The pulmonic second sound is accentuated in those cases in which there is a significant left-to-right shunt, and is especially prominent in those individuals with pulmonary hypertension. A snapping mitral first sound may be present with coexisting mitral stenosis. There is no characteristic murmur of atrial septal defect. In some cases a murmur is never heard; in others it may disappear with changes in the relative pressures in the atria. In the uncomplicated condition, in the majority of individuals there is a systolic murmur, best heard in the second or the second and third interspaces to the left of the sternum. The genesis of the murmur is problematic. By reason of cardiac events it should, if due to the flow of blood through the defect, be presystolic in time. Taussig's<sup>22</sup> impression is that it probably originates in atrial diastole which coincides with early ventricular systole. Bedford, Papp and Parkinson<sup>19</sup> accept the explanation that dilatation of the pulmonary conus and pulmonary artery gives rise to a relative stenosis of the pulmonary valve and thus a murmur is produced. The murmur is likely to be harsh and loud. It is transmitted over the precordium and often can be heard posteriorly. Great dilatation of the pulmonary artery may so stretch the valve ring that incompetence results, and a diastolic murmur may develop in the pulmonic area or be heard at the apex. Complicating rheumatic infection gives rise to mitral valve murmurs; with the development of stenosis, the typical mid-diastolic rumble is heard.

The combination of a systolic murmur at the base and a diastolic or systolic and diastolic murmurs at the apex is very suggestive of the presence of atrial septal defect complicated by mitral stenosis (Lutembacher's syndrome). However, even though the conventional roentgen studies appear to confirm the impression, one should be wary. We recently studied a patient who fulfilled all the clinical criteria for a diagnosis of Lutembacher's syndrome. At autopsy there were no cardiac lesions. Marked pulmonary arteriolar sclerosis was present. We are aware of two similar experiences.<sup>24, 25</sup>

The blood pressure in uncomplicated atrial septal defect is said to be low. Actually, in most cases during the period of adequate compensation the pressure is within normal limits.

The presence of cyanosis is indicative of (1) an extremely large defect, creating virtually a single chamber and allowing free mixture of arterial and venous blood; (2) coexisting pulmonary stenosis and a resultant right-to-left shunt; (3) increased pulmonary resistance due to changes in the pulmonary vascular tree and reversal of flow; (4) the presence of pulmonary infection, such as pneumonia, or (5) acute failure of the right heart, with rise in pressure and reversal of flow. In uncomplicated defects, although there is probably some degree of abnormal arterial oxygen unsaturation in most cases, cyanosis is not a feature unless failure supervenes. This

is not necessarily terminal, for compensation may be regained and cyanosis disappear. Chronic cyanosis in patients with the defect unassociated with pulmonary stenosis may be marked but usually is slight to moderate in degree.

Clubbing of the digits is appreciable in those patients with long standing right-to-left shunt through the defect.

Paradoxic embolization as a sign of atrial septal defect was stressed in the older literature. That it has occurred cannot be denied, but it is an uncommon complication. It signifies the presence of a systemic venous or of a right atrial thrombus and a right-to-left shunt.

*Symptoms:* Too much stress has been laid upon the proposition that patients with uncomplicated atrial septal defects often manifest no symptoms until the third or fourth decades. Although this is true of many individuals, it does not hold for the majority. Careful questioning will bring forth evidence of disturbed cardiac dynamics in most such individuals.

Shortness of breath is an almost constant symptom. It is noteworthy that adult patients will often date their respiratory difficulty from the relatively recent past, whereas the parents of affected children will often date their awareness of puffing on exertion from the time of early play. This might indicate that dyspnea becomes so habitual that it is not complained of during early adult years and only when it becomes very marked is it a matter of concern to the adult individual. Limitation of exercise tolerance is characteristic. This does not always mean easy fatigue; it may be due to severe dyspnea on effort, particularly in young patients. In older individuals, the element of fatigue is usually present. Episodes of paroxysmal tachycardia are not uncommon. They tend to develop following exertion in older patients but may occur at any time in young children. Hemoptysis occasionally occurs, in all probability consequent upon pulmonary hypertension.

Chest pain is found in an appreciable number of patients. It was present in four of 10 of our operated series, and was frequently mentioned by others with the proved defect. It may be explained on the basis of decreased coronary flow incident to increased right heart pressure. Excessive perspiration is frequently noted in young children, as it is in other forms of congenital cardiac disease.

*Rheumatic Complication:* Evidence of valvulitis and endocarditis is found more frequently in association with atrial communications than in any other congenital cardiac malformation, and is indistinguishable from the sequelae of the rheumatic state. A history of rheumatic fever is infrequently elicited, a fact which has led some to believe that the endocarditis is congenital in nature. Inasmuch as a history of rheumatic fever cannot be elicited in at least 50 per cent of those with mitral stenosis without atrial communication, this argument has little force.

Mitral stenosis developing in the presence of an atrial septal communication gives rise to a condition designated as the Lutembacher syndrome.<sup>26</sup>

The effect of the stenosis is to increase pulmonary flow at the expense of systemic (left-to-right shunt).

*Clinical Course:* It is difficult, in dealing with a malformation such as uncomplicated atrial septal communication, to limn a typical history. There is such a wide variation in the manifestations that a number of courses must be described. First, there is the individual who lives a normal life and dies of intercurrent illness or old age. He concerns us only in that he serves to give many a false impression of the seriousness of the condition. So sanguine is the medical mind that one happy recovery or survival from a hitherto fatal condition causes us to lose some of our healthy respect for the condition. Next, and at the opposite extreme, is the infant who has a large defect and dies relatively soon after birth. He often appears normal at the time of delivery but shortly thereafter—in hours, days or weeks—exhibits cyanosis which may be intermittent or continuous. A murmur, systolic in time and maximal in the pulmonic area, is heard on the first examination, or perhaps not until several weeks later. If late, the time of its discovery does not always mean that it was not present at birth. Routine examination of the infant's heart often leaves much to be desired. The mother notes that the infant's respirations are rapid and noisy and that he becomes short of breath during feeding. He may choke or gag. His cardiac impulse is prominent; this may be one reason for his first visit to the physician, because his mother recognizes it as abnormal. Too often the physician will acknowledge the presence of a congenital cardiac defect but will assure the parents that it will be outgrown. As time passes it is obvious that the infant is not progressing normally. His weight gain is poor, and he is underdeveloped and subject to frequent respiratory infections. The poor development need not be attributed to the intracardiac shunt and tissue anoxia, although these are no doubt factors. Simple lack of sufficient caloric intake is probably as important. The effort of feeding is so taxing on the slim reserve that only minimal needs are met. The reserve is in time exhausted and, after a period of increasing heart size—occasionally to enormous proportions—and of progressive cardiac failure, the infant dies.

More fortunate is the infant with an adequate reserve. He survives the initial period of stress, and the ability of the heart to compensate for its deficiency appears to improve as time passes. Weight gain accelerates and motor development, although delayed in initiation, progresses satisfactorily. With acquisition of increasing mobile powers, the parents notice that the child becomes short of breath rather easily and perhaps tires after what they consider to be a brief effort. If he had been cyanotic early, by this time it may no longer be noticeable, or may appear transiently only on exertion. Or, during this period, cyanosis may appear for the first time. Prominent in the history of these children are respiratory infections. It is not unusual to elicit the information that the patient had pneumonia three or four times during infancy and early childhood, and was always subject to "chest colds" and bronchitis. Careful questioning of the parents and the attending phy-

sician frequently raises the suspicion that the "pneumonia" was actually an episode of congestive heart failure. As the individual grows older his activities are limited by the power of his heart to maintain output. Some die in early childhood, others in late. Some survive to adolescence and older as chronic invalids, each successive year speaking not for the benignity of the condition but for its brutality.

The final group to be considered is those patients who reach early adult or middle years without symptoms or what, in the clinical summing up, is referred to as minimal disability. Sometimes the lack of symptoms and disability may be accounted for by the fact that these patients have learned early in life of the existence of a cardiac malformation and have been careful to nurture their reserve. These individuals, when they come to our attention, detail a recent history of progressive intolerance of exertion, shortness of breath, palpitation, paroxysmal nocturnal dyspnea, etc., or show gross evidence of cardiac failure. Often the female patient has experienced parturition without difficulty; perhaps she has borne a number of children. But with progression of time she has noted increasing ease of fatigue and dyspnea, and has become more and more conscious of her heart, due to sudden bouts of tachycardia or increasing force of the beat. Or perhaps, during her last pregnancy, there was gradual or sudden onset of frank heart failure, which only prompt and adequate medical attention enabled her to survive. Eventually these patients deteriorate to the point where ordinary methods of treatment are of no avail and they die, death occurring at a relatively early age.

In the light of our present knowledge it is impossible to assign to any of the forementioned groups a numeral of frequency. It is our opinion that the majority of individuals with the defect are significantly affected. In consulting many of the reviews of the condition, one receives the unfortunate impression that the lesion bears a relatively good prognosis. This stems from the fact that in various series the average age of death is high when compared with that of many other cardiac malformations. However, prognosis should be judged on an absolute rather than on a relative scale. Omitted, too, from consideration is the fact that so many of the patients who survive to a respectable age find their prolonged existence a burden.

*Diagnosis:* The diagnosis of uncomplicated interatrial communication is to be suspected in a patient exhibiting the signs and symptoms and one of the courses described.

The electrocardiogram is not characteristic. It may be normal. The abnormal findings consist of P wave changes, arrhythmias, right heart strain and right bundle branch system block. P wave deformities, notching and peaking are not constant in isolated atrial septal defect but may frequently be observed in combined lesions such as the Lutembacher syndrome and pulmonary stenosis. Arrhythmias such as auricular premature systoles, auricular tachycardia and auricular fibrillation are occasionally found, particularly in individuals in whom mitral stenosis coexists. Right heart strain



is found in the course of the uncomplicated defect following the development of pulmonary and right ventricular hypertension.<sup>27</sup> It almost always occurs in cases with the defect plus pulmonary stenosis. The appearance of right heart strain in an infant suspected of having an atrial septal defect should arouse the suspicion of the presence of pulmonary stenosis as a complicating factor. We recently studied two very young patients with the clinical and roentgen features of atrial septal defect. In each case its presence was confirmed by passage of the catheter into the left atrium. In neither case could the pulmonary artery be entered, but right ventricular hypertension was present. Because of their progressively downward course, surgical correction of the atrial defect was felt necessary. At operation both were found to have pulmonic valve stenosis in addition to the atrial communication. There is a high incidence of right bundle branch system block in isolated atrial septal defect and in Ebstein's malformation with a patent foramen ovale. This was observed in four of the 10 cases considered in this paper, and in Wood's<sup>14</sup> series was present in a majority of patients. Its mechanism is not clear.

Radiography contributes valuable information (figure 1). Because of the increased pulmonary flow there is an increase in the vascular shadows in the lung fields. The right and left pulmonary arteries are dilated. The heart is usually enlarged in its transverse diameter, although early it may be grossly normal in size. As a rule, in older patients the enlargement is pronounced. The increased inflow of blood into the right atrium causes this easily distensible chamber to assume a prominent portion of the heart shadow to the right of the spine. The right ventricle is also enlarged and encroaches upon the retrosternal space. The main pulmonary artery segment of the left cardiac border—so often erroneously referred to as the pulmonary conus—is dilated, frequently to a marked degree. Its pulsations and those of the right and left branches are usually increased, although they may be normal. We have found no constant relationship between the degree of pulmonary hypertension and the amplitude of pulsation. Cardiac pulsations, especially of the right border, are increased in prominence in most cases, especially those of the atrial segment. The aortic knob frequently appears small in the AP view, due in part to rotation of the heart. Aortic pulsations are normal.

Complicating lesions alter the roentgen appearance. Pulmonary stenosis, for example, is accompanied by diminished pulmonary vascular markings. In the presence of mitral stenosis the pulmonary artery will be larger than in uncomplicated atrial communication, although in the individual case this point is of no differential value. There will be evidence of left atrial enlargement only if the atrial defect is not large enough completely to relieve the increased left atrial pressure.

These criteria, clinical and roentgenologic, are sufficient in some cases for diagnosis. In the light of possible surgical intervention in any individual case, however, the diagnosis should always be confirmed by special study.



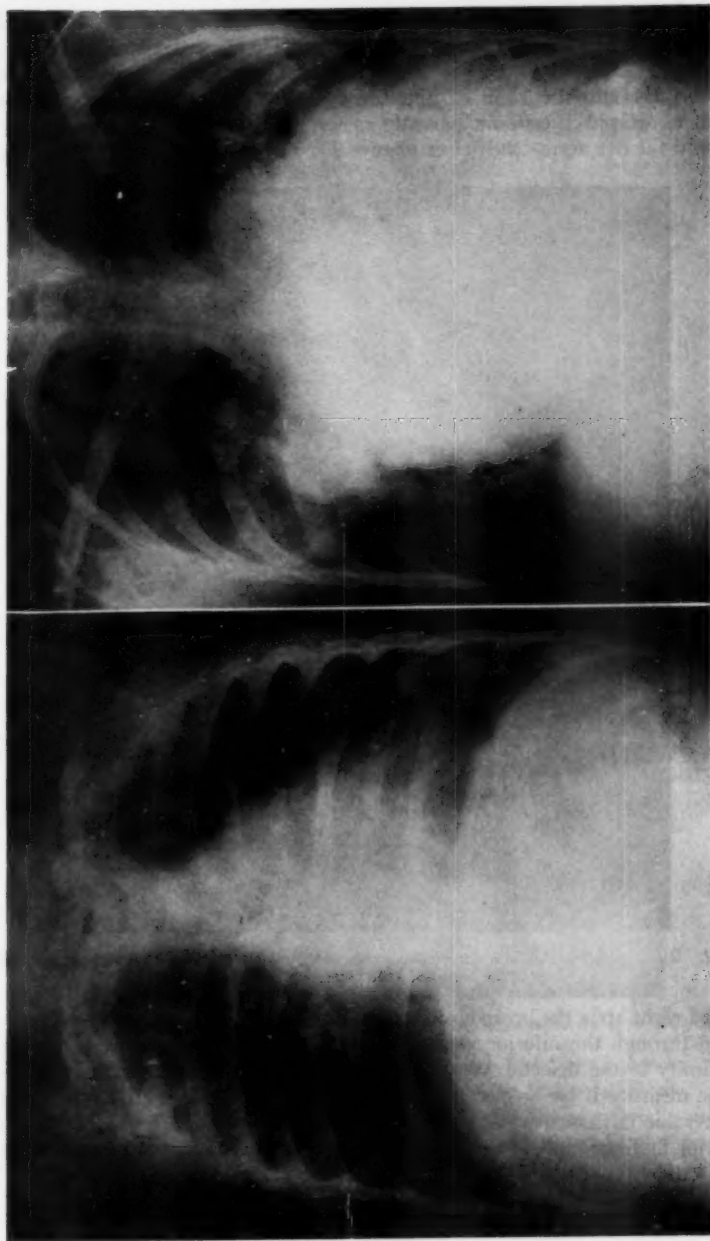


FIG. 1. (left) A-P x-ray of child, age 2 years, with interatrial septal defect, uncomplicated. (right) A-P x-ray of adult with uncomplicated atrial septal defect.

By means of angiocardiology we have been able to demonstrate atrial septal communications in a high percentage of small patients. In the uncomplicated cases our success is due to the fact that we inject the radiopaque dye directly into the right atrium through a short, relatively large bore catheter. Rapid injection apparently raises right atrial pressure sufficiently to shunt the dye across the defect (figure 2). In older patients with greatly



FIG. 2. Right posterior oblique angiogram, showing shunt of dye from right to left atrium through an atrial septal defect.

dilated right atria the procedure is of little value unless the catheter is introduced through the inferior vena cava and its tip by chance placed in close proximity to the defect. We do not employ angiocardiology as a diagnostic measure if we suspect atrial septal defect. However, it has been of great value in demonstrating the lesion in small infants with clinically nondescript findings, and in certain other individuals with conflicting evidence from other studies.

Cardiac catheterization is the most suitable method of definitively diagnosing atrial septal defects ante mortem without resorting to surgical exploration. The discovery of an increased oxygen content of the right atrial blood can mean only that there is a shunt of arterial blood into that chamber. This might be due to the emptying of one or more of the pulmonary veins



FIG. 3. Catheter tip traversing an interatrial septal defect from right to left atrium.

into the right atrium or into the venae cavae, or passage of blood from the left atrium through a septal communication. The former anomaly, like so many "rare" congenital cardiovascular defects, is encountered with unexpected frequency. Fortunately we have been able to make the diagnosis of this anomaly in a large number of cases by passing the catheter directly

into the pulmonary field from the right atrium. In many cases a coexisting atrial communication is also demonstrated.

In a large proportion of cases subjected to catheterization the diagnosis is substantiated by passing the catheter from the right to the left atrium through the defect (figure 3). This is relatively easy when the inferior caval route is used. The relation of the septum to the orifice of this vessel is such that by slight manipulation of the catheter it will traverse the defect. In many cases no manipulation is necessary, and the left atrium is entered immediately on passage of the catheter.

Pulmonary artery pressure determined during catheterization is of great diagnostic and prognostic value. If an atrial communication is demonstrated by passage of the catheter into the left atrium, and if the pulmonary arterial pressure is significantly lower than that of the right ventricle, one is dealing with a complex in which pulmonary stenosis is the important lesion. If an atrial communication is proved and the pulmonary artery pressure is high, the prognosis is grave.

Cardiac exploration may be considered as a diagnostic procedure in some individuals with congenital cardiac malformation in which the other methods, ordinary and extraordinary, have been tried without conclusive results and in whom it is vital, because of their condition, to arrive at a diagnosis and to institute whatever surgical treatment is possible. In the case of suspected atrial septal communication, the introduction of a finger into the atrium via the atrial appendage allows competent investigation of the integrity of the septum. The surgeon must, however, be thoroughly acquainted with the anatomy of both atria, particularly with the location of the orifices of the pulmonary veins, venae cavae and coronary sinus. In addition, he must be familiar with the mitral and tricuspid valves, for such is the relationship of the intracardiac structures that the inexperienced exploring finger might easily mistake a high ventricular septal defect for one between the atria.

*Differential Diagnosis:* On clinical and roentgen data alone, atrial septal defects may require differentiation from a number of conditions, among which are: patent ductus arteriosus with only a systolic murmur, high ventricular septal defect, isolated pulmonary stenosis, idiopathic dilatation of the pulmonary artery, and Ebstein's malformation of the tricuspid valve. Final diagnosis may depend upon cardiac catheterization in all except Ebstein's malformation, in which angiocardiology is more frequently diagnostic.

#### SURGICAL CONSIDERATIONS

This portion of the presentation concerns itself only with those cases of interatrial communication in which the defect itself is the major cause of cardiac disability. Thus, no consideration is given to pulmonic stenosis with a patent foramen ovale. Valvulotomy alone is sufficient to correct the right-to-left shunt. It is possible, particularly in older individuals, that functional closure of the foramen ovale will not occur following valvulotomy,

and that a left-to-right shunt may develop. In such an event, a second operation to close the foramen would be justified if a new complex of symptoms and signs appeared. This same principle applies in those cases of mitral stenosis associated with a patent foramen ovale. If, however, the atrial communication is an actual defect and of significant size, a mitral commissurotomy and closure of the defect should be accomplished at the one operation. Naturally we are not concerned, either, with those atrial communications which function in a compensatory manner, as in Ebstein's malformation of the tricuspid valve or complete pulmonary venous drainage into the right atrium or venae cavae.

The proper surgical procedure for closure of an interatrial septal defect must be one which (a) is technically feasible; (b) does not involve introduction of a prosthetic device into the heart, and (c) will obliterate the defect without causing adverse effects on cardiodynamics. A number of experimental and clinical approaches to the problem have been made.

Cohn<sup>28</sup> produced defects in dogs by forcing a clamp through the atrial septum. Two weeks later, the right atrium was exposed. The wall of the atrium was invaginated to come into contact with the defect and a stitch was placed through the atrial wall, the septum at the periphery of the defect, and again out through the atrial wall. This was then snugged and tied. A second suture was placed if possible. Next, a wire threaded on a needle was placed in the atrial wall and made to encircle completely that part now attached to the septum, entering and emerging at the same point. A running silk suture was then placed in the atrial wall to encircle the portion attached to the defect and carried up to the point of emergence of the wire. Tightening the running stitch served to bring adjacent areas of the atrial wall together and to bury the portion closing the defect. The wire was then pulled through the atrial muscle with a tonsil snare, cutting off that portion and allowing it to remain as a free patch over the defect. The small hole occupied by the snare was closed by continuing the running silk suture (figure 4). Cohn successfully performed the procedure in five of eight dogs, and when they were killed after a month a collection of tissue was noted on the septal wall made up of atrial muscle and scar tissue. He concluded that this procedure might be simpler to perform on a human being with the defect because the right atrium would be dilated.

Murray<sup>29</sup> in 1948 reported closure of an atrial septal defect in a 12 year old child. Silk sutures were introduced to the right of the aorta and pulmonary artery and directed out posteriorly through the area between the superior vena cava and the right pulmonary veins. They were tied together posteriorly and drawn taut anteriorly. The right atrium diminished in size one-half in two minutes. The sutures were then tied firmly and the chest was closed. It was stated that the patient's general health was much improved. Further information on this patient is derived from the paper of Keith and Forsyth.<sup>20</sup> Cardiac catheterization 14 months postoperatively showed a substantial left-to-right shunt and significant right heart hyper-

tension. She had had at least one episode of cardiac failure during this period. Cardiac x-ray showed some generalized decrease in size.

Martin and Essex<sup>30</sup> produced atrial septal defects in dogs. To close them they introduced a sheet of Polythene covered with an inverted segment of vein into the right atrium in close apposition to the defect. Three silk

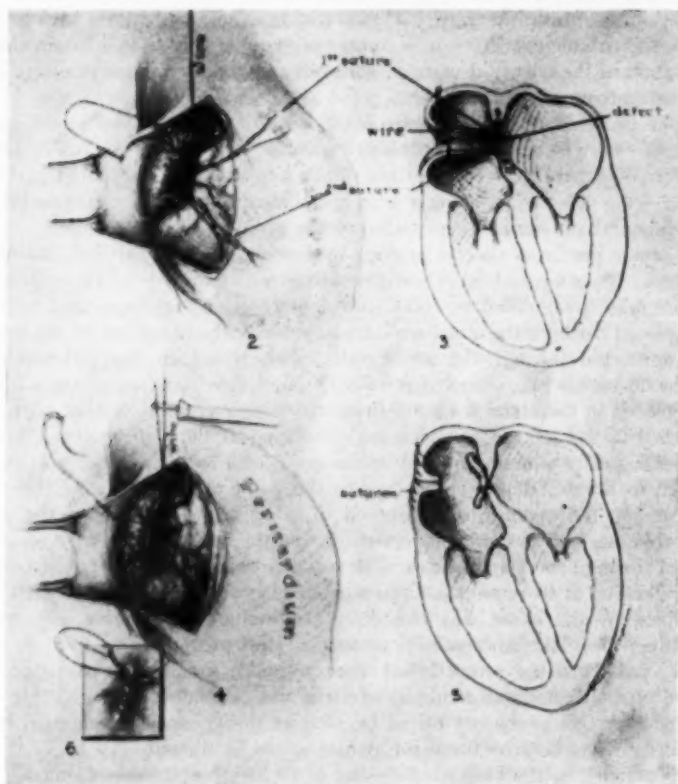


FIG. 4. Illustration of Cohn's technic for experimental closure of an interatrial defect. (Reproduced through courtesy of Cohn, R., *Am. Heart J.* 33: 453, 1947.)

sutures with straight needles attached to the graft were introduced into the atrium separately through a small incision. The needles were brought out of the chamber at points in the plane of the atrial septum. The graft was found to have become endothelialized in two weeks.

Dodrill<sup>31</sup> devised a clamp which would allow approximation of the atrial walls against the septum, with exclusion of a central portion (figure 5).

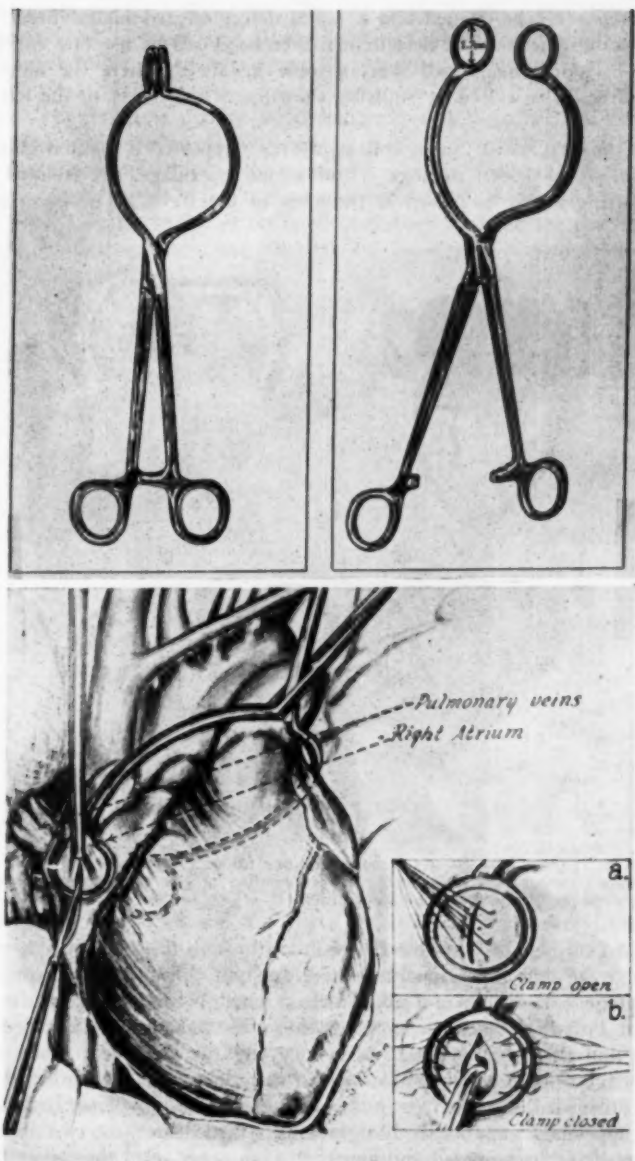


FIG. 5. (above) Clamp devised by Dodrill for creation and closure of interatrial septal defects. (below) Clamp in position and technic of creation of defect. (Reproduced through the courtesy of Dodrill, F. D., *J. Thoracic Surg.* 18: 652, 1949.)



This area could be opened and a septal defect created under direct vision in a bloodless field. The defect could then be closed by use of a continuous suture. Dodrill mentioned that in some instances, where the defect was large, it could be closed by suturing the edge of the defect to the left atrial wall.

In January, 1950, Swan and associates<sup>22</sup> reported a method of closure of atrial septal defects in dogs. Both atrial appendages are isolated and a purse-string suture is placed at the apex of the right. The eye end of a

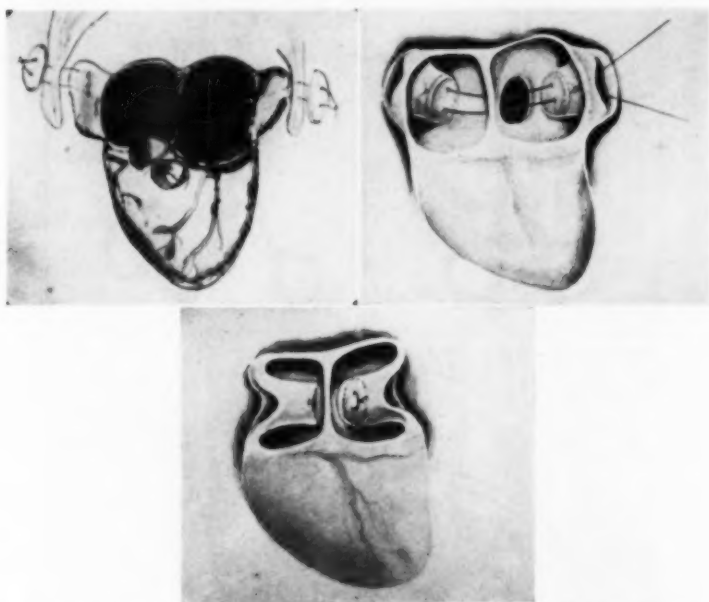


FIG. 6. (upper left) Swan's technic. Sutures through both appendages and threaded on buttons. (upper right) Beginning of invagination of the appendages. (below) Appendages meeting in the defect and sutures tied.

standard surgical probe is then introduced through the loop, into the atrium, through the defect previously created, and out through the tip of the left appendage. Two ends of a silk suture on which is threaded a circular button of stiff Polythene lined on its inner side with Gelfoam are attached to the probe and this is now withdrawn, snugging the Gelfoam against the left appendage tip and starting inversion of the appendage. A similar preparation is threaded onto the free ends of the silk sutures now emerging from the right appendage and, by firmly tightening a throw knot, the two appendages are gradually invaginated and approach each other until they meet through

the defect (figure 6). Swan has adapted this procedure for clinical application and has operated upon several patients with the condition.<sup>22</sup>

Hufnagel<sup>24</sup> has closed experimentally produced atrial septal defects by means of plastic buttons. Two opposing nylon buttons, one with small teeth which insert into a shallow peripheral groove on the other, are threaded upon a pencil-like instrument consisting of a solid inner rod inserted into a hollow outer rod. Turning these rods in opposite directions will separate the buttons; turning them in the reverse direction will bring them together (figure 7). Closure of the defect is accomplished by inserting the holding rods with buttons in place into the atrium, the correct size of the button

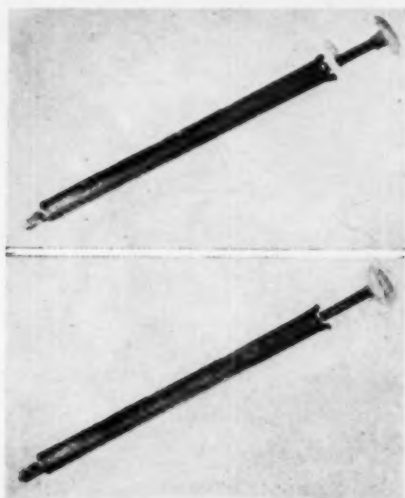


FIG. 7. Hufnagel's instrument for placement of plastic buttons to close interatrial septal defect. (Reproduced through the courtesy of Hufnagel, C. A., *Bull., Georgetown Univ. M. Center* 4: 137, 1951.)

being first determined by direct palpation through the atrial appendage. The two buttons are separated and the distal one, of diameter larger than the defect, is slipped through the defect and, by traction on the holder, the teeth are engaged in septal tissue. The opposing button is then tightly screwed onto the first, the holder disengaged and the appendage closed. Complete closure of the defect has been verified in the sacrificed animals.

Each of these procedures has certain objectionable features. Cohn's method invites thrombus formation on the rough, nonendocardial surface of the patch of atrial wall which presents in the right atrium. Furthermore, it is unnecessary to use such a free patch. Two sutures can scarcely be expected to close securely a clinical defect. Murray's technic has the great

disadvantage of being blind; in addition, apposition of the margins of the defect could not be expected in all cases, and the shunt would not be entirely eliminated. Insertion of the finger into the atrium through the appendage to guide placement of the sutures would serve to minimize the former objection. The technic of Martin and Essex introduces a foreign body into the heart, and it is questionable whether the device would be effective in any but very small defects. Dodrill's clamp would no doubt seriously interfere with atrial flow in many cases and might also cause production of serious arrhythmias. For clinical application in the case of a large defect it is

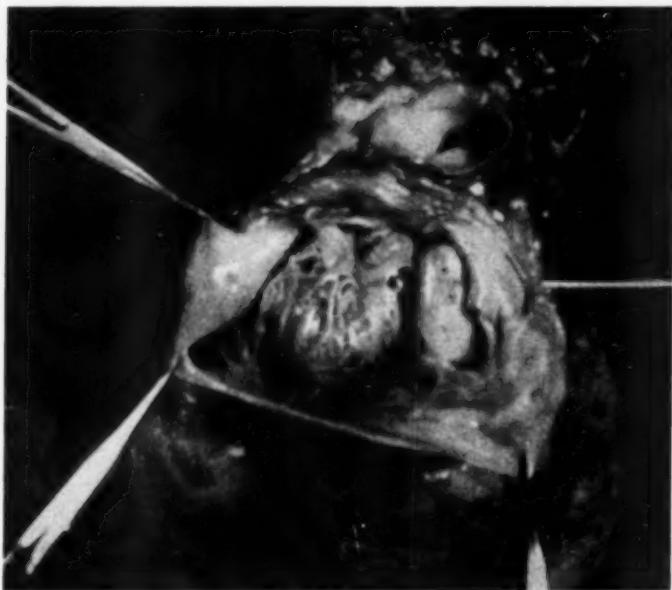


FIG. 8. Autopsy specimen of heart following Swan technic. Defect is not completely obliterated and the appendages have not grown fast to its margin.

questionable whether a clamp of proper size could be placed with any degree of safety. Swan's technic is relatively simple and certainly beneficial in some cases. There is a serious question, however, in regard to healing of the apposed appendages to the edge of the defect. In one of our patients subjected to this method, who died 13 days postoperatively, no adhesion was found between the appendages and the septum, and a large defect remained (figure 8). Too, large defects would require application of large buttons, and in some cases this would cut down the lumen of the relatively small left atrium to dangerous or lethal limits. A third objection is that eccentrically

placed defects cannot be obliterated in this manner. We feel that Swan's technic has definite value in a patient operated on from the left side in whom an atrial defect is discovered and who appears to be in such poor condition that the procedure detailed below cannot then safely be performed.

Our experience in the surgical correction of atrial septal communications embraces 10 cases. Not all of the patients were definitively treated, but each contributed to the operator's knowledge of the condition as a surgical problem, and none can fairly be omitted from the series.

#### CASE REPORTS

*Case 1.* Female, age 29. Chronic fatigue, precordial pain, paroxysmal tachycardia, dyspnea for six months. One episode of cyanosis. Atrial septal defect closed by Swan technic, performed from the left side. Relieved of her symptoms in part, but evidence of a shunt remains.

*Case 2.* Female, age 31. Dyspnea and palpitation for five years. Several episodes of hemoptysis. Cardiac catheterization; atrial septal defect. Left exploratory cardiectomy; no atrial septal defect was found. Postoperatively she became cyanotic and died on the third day. At autopsy, a 1 cm. defect in the superior portion of the atrial septum.

*Case 3.* Male, age 37. Cyanosis, dyspnea and diminished exercise tolerance since infancy. Exploratory cardiectomy: no evidence of pulmonary stenosis or of ventricular septal defect. Large atrial septal defect. Closed at least partially by Swan technic. Postoperatively, increasing cyanosis and downward course. Re-operated and closure taken down. Died two days later. Autopsy: large atrial septal defect; drainage of all pulmonary veins into the right atrium.

*Case 4.* Female, age 38. Weakness, easy fatigue, dyspnea for eight years. Cardiac catheterization: atrial septal defect. Closed by Swan technic. Some relief of symptoms, but evidence of partial persistence of shunt.

*Case 5.* Male, age 24. Dyspnea, progressive, for seven months. Moderately severe cardiac failure. Improved on medical therapy. Atrial septal defect diagnosed by cardiac catheterization. Mitral stenosis also present. During induction of anesthesia, ventricular fibrillation developed. Electroshock and manual massage of heart induced weak beat. Finger commissurotomy performed quickly. Cardiac action improved for short while, but then failed. Autopsy: mitral stenosis; 5 cm. atrial septal defect.

*Case 6.* Female, age 47. Lutembacher's syndrome. Mitral commissurotomy at another hospital. Atrial septal defect closed by Swan technic one year later. Died 13 days postoperatively. Autopsy: only a portion of the defect closed by the invaginated appendages. No healing to the margins of the defect (figure 8).

*Case 7.* Female, age 51. Lutembacher's syndrome. Mitral commissurotomy. Large atrial septal defect not closed because two pulmonary veins found to enter right atrium.

*Case 8.* Female. Large atrial septal defect discovered during course of intended mitral commissurotomy. Closed by Swan technic one year later. Appeared to be progressing satisfactorily but died two days postoperatively. No autopsy.

*Case 9.* Female, age 47. Lutembacher's syndrome, with only moderate mitral stenosis. Mitral commissurotomy. Atrial septal defect not closed because patient's condition became precarious. Died day following operation. At autopsy, 3 cm. atrial septal defect.

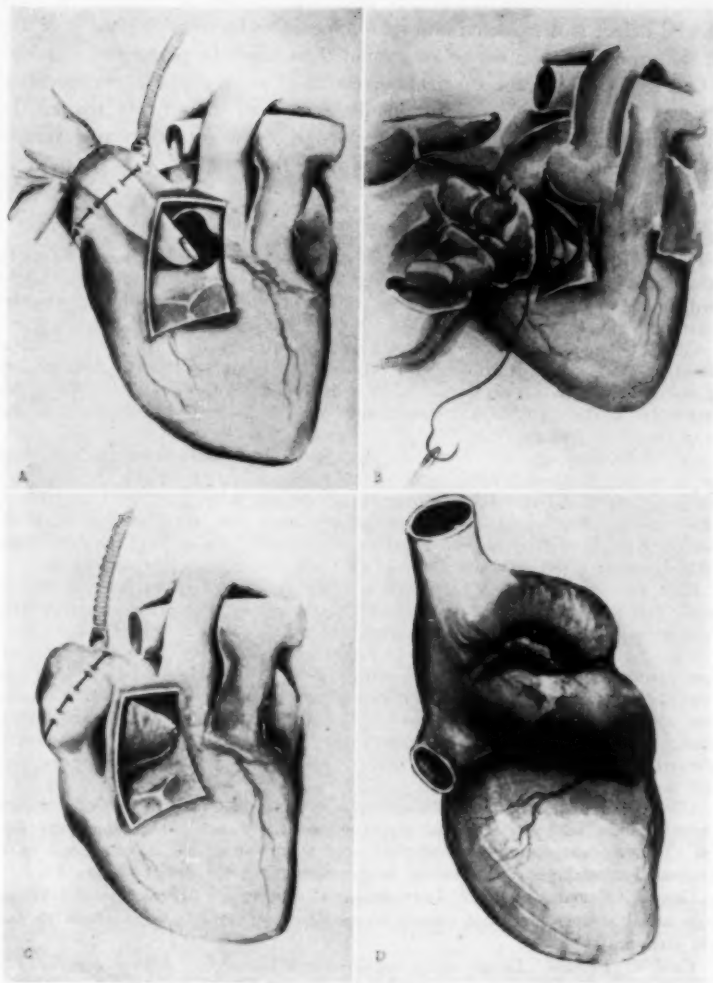


FIG. 9a. Technic of atrio-septo-plexy. Index finger introduced through right atrial appendage palpates margin of defect. b. Sutures placed through wall of atrium and margin of defect, guided by intracardiac finger. c. Defect entirely obliterated. Right atrial wall invaginated. d. View of right atrium showing closure completed and adequacy of remaining chamber.

The generally unsatisfactory outcome in these nine cases persuaded us that another or other solutions than those presently available must be sought. Our experience made it clear that these patients are in a precarious state, and that any operative intervention is extremely risky. Success depends upon the operator's ability adequately to close the defect with dispatch.

It occurred to one of us (CPB), in contemplating the heart of the last patient at autopsy, that here was a condition in which there was a deficiency of tissue in one area (the defect), while in close proximity there was an excess of tissue (the wall of the dilated right atrium). It seemed obvious that advantage might be taken of this situation. The heart was reconstructed with sutures and the left index finger inserted into the right atrium through the atrial appendage. Sutures were now placed through the right atrial wall and, guided by the intracardiac finger, through the margin of the defect, and again out through the atrial wall, bringing the wall in close approximation to the margin of the defect. In this manner the right atrial cavity was completely excluded from communication with the left. The intracardiac finger was removed from the heart, and the tip of the atrial appendage, now communicating directly with the left atrium, was oversewn. There was no obstruction to the orifices of the venae cavae, and the atrial cavity, although much reduced in size, appeared adequate (figure 9). This procedure was considered entirely feasible for use in a living patient, and the operation was successfully accomplished on January 11, 1952.

TABLE II  
Cardiac Catheterization Data (Case 10)

Site	Preoperative*		Postoperative	
	Pressure (mm. Hg)	Oxygen (Vol. %)	Pressure (mm. Hg)	Oxygen (Vol. %)
PVC		16.2		
RPA	90/40 (65)†	16.0	45-50/30-35	(40) 11.9
MPA		16.2		11.5
RV (outflow)	90/10 (55)	15.4	45-50/30-35	(40) 11.7
RV (mid)				11.5
RV (low)		15.9		11.9
RA (low)	10/2 (5)	17.2	10/2 (5)	11.99
RA (mid)		14.6		11.99
RA (high)		12.2		9.95
LA	13/4 (2)	17.3		
Systemic artery		16.9		14.5
Capacity		18.0		17.6
Saturation		94%		82.4% (17 days post-op.) 95.0% (3 mos. post-op.)
Oxygen consumption	190 c.c./min.		177 c.c./min.	
Systemic blood flow	4.05 l/min.		5.9 l/min.	
Pulmonary blood flow	17.3 l/min.		5.9 l/min.	
Shunt	13.2 l/min. (left-to-right)		None	

\* Preoperative data kindly supplied by Dr. Bernard Brofman, Cleveland, Ohio.

† Figures in parentheses indicate mean pressure.

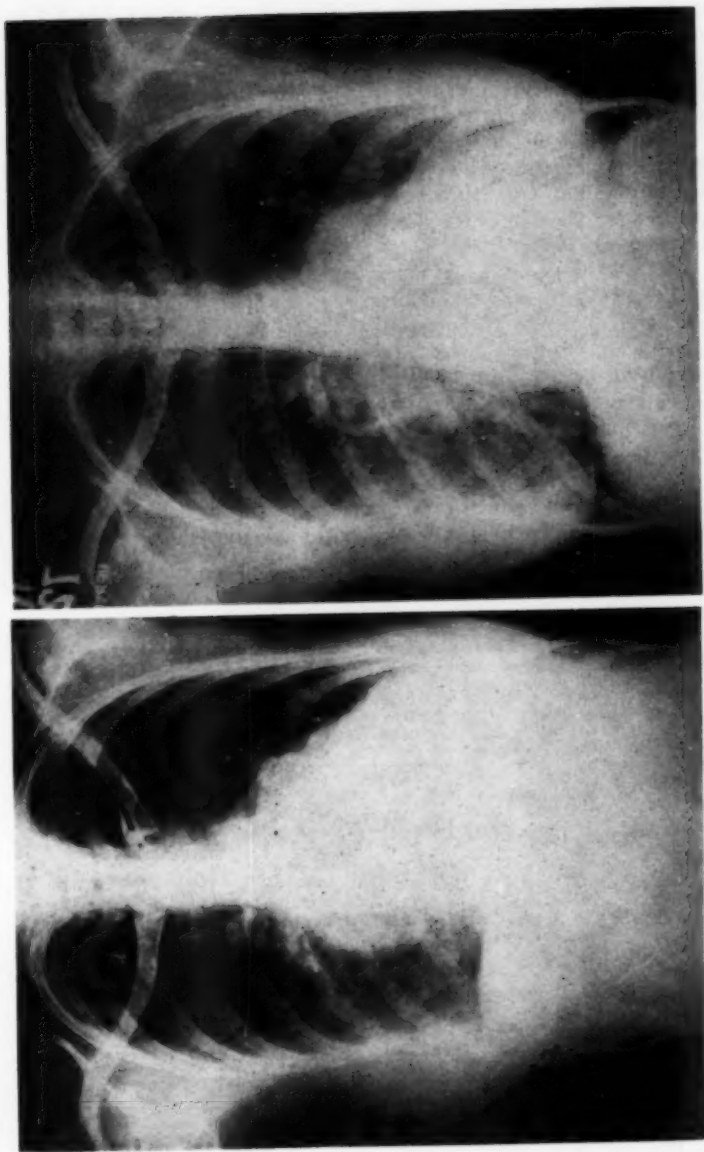


FIG. 10. (*left*) Preoperative x-ray of heart of patient 10. (*right*) Postoperative x-ray of heart, showing some decrease in transverse diameter.



*Case 10.* Female, age 38. A heart murmur had been present from birth. One year prior to admission dyspnea on exertion developed, becoming progressively more incapacitating. Three months before admission, cardiac catheterization was performed at another hospital. The catheter passed through an atrial septal defect and the blood oxygen studies demonstrated a large left-to-right shunt (table 2).

On physical examination the heart was enlarged. There was no thrill. The pulmonic second sound was markedly accentuated. A rough, grade III systolic murmur was heard in the third left interspace.

The electrocardiogram showed marked right ventricular hypertrophy and strain. On fluoroscopy the pulmonary vascular markings were greatly accentuated. The

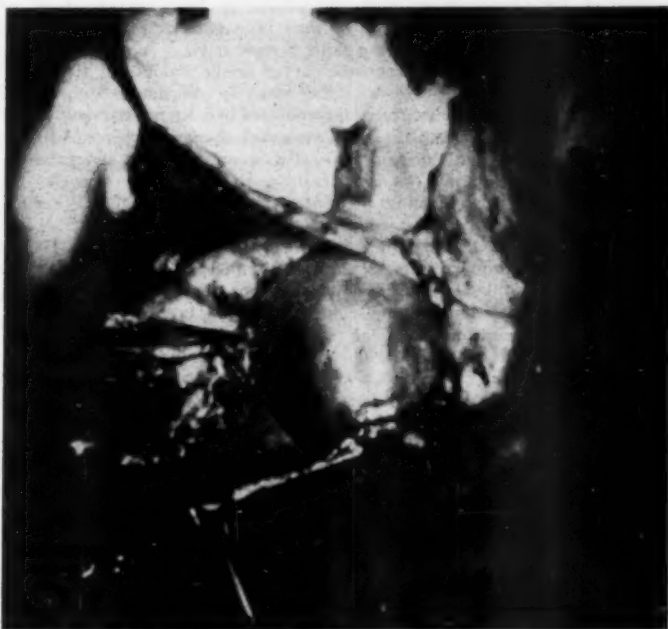


FIG. 11. Photograph of heart of patient 10 after atrio-septo-pxy had been completed. The chamber is now relatively normal in size and there has been no compromise of caval inflow.

heart was enlarged to right and left. The right auricle and ventricle were very prominent. The left cardiac chambers were of normal size. The main pulmonary artery was hugely dilated, and the right and left pulmonary arteries were very prominent. Pulsations were increased. The aorta appeared relatively small.

At operation on January 11, 1952, the interatrial septal defect was completely obliterated by the technic to be described. The early postoperative course was marked by much difficulty with regard to retained bronchial secretions. Bronchoscopy was necessary on four successive days. On the second postoperative day auricular fibrillation developed but was readily controlled. On the sixth day a right

paravertebral thoracic nerve block, T3 to T8 inclusive, was performed because of persistent right chest pain.

Throughout the remainder of the hospital stay the patient's condition progressively improved, although there was persistence of râles, bronchial breathing and dullness at the right base. At no time was there cyanosis or venous distention. No murmur was audible, and there was a significant decrease in the intensity of the pulmonary second sound.

Fluoroscopy before discharge showed the pulmonary vasculature to be unchanged, but there was a decrease in the transverse diameter of the heart (figure 10). Cardiac catheterization indicated that there now was no left-to-right shunt (table 2). The physiologic data and their implications will be the subject of a separate report.<sup>25</sup>

*Technic of Atrio-Septo-Pexy:* With the patient in the supine position, an incision was made through the right fourth interspace anteriorly. The pericardium was incised longitudinally anterior to the right phrenic nerve. A purse-string suture of No. 2 braided white silk on an atraumatic curved needle was placed about the base of the right atrial appendage, which was rather small in comparison with the hugely distended right atrium. The sutures were incorporated in a Rumel-Belmont tourniquet for easy hemostatic control. A Satinsky porto-caval clamp was placed at the base of the appendage and a 1.5 cm. incision made at its apex. The left index finger was inserted through this incision into the right atrium as the clamp was removed. Hemostasis was maintained by tightening the purse-string suture. Digital exploration revealed a large atrial septal defect, approximately 4 cm. in diameter. Surrounding it was a definite ridge of septal tissue, somewhat deficient posteriorly. The mitral valve was located by passing the finger through the defect into the left atrium. It may have been slightly thickened but certainly was not stenotic. Had it been, either digital or instrumental commissurotomy could easily have been performed from this right sided approach. The orifices of the pulmonary veins were all found in the left atrium. The venae cavae and the tricuspid valve were found to be normal.

By invaginating the right atrial wall with a gauze pad held in a pair of forceps, it was found possible to introduce a 1.8 cm. long half-circle needle swedged on No. 2 braided silk through the atrial wall, through the rim of tissue surrounding the defect and out again. A series of interlocking mattress sutures was thus applied, interrupting the continuity every fourth or fifth bite with a knot. The intracardiac finger proved to be an excellent guide to placement of the needle in the septal tissue. After picking up the glove on this finger with the needle point a number of times, it was removed and the rest of the operation performed with a bare finger in the heart.

Finally, the atrial wall was completely affixed to the margin of the defect. The finger now extended through the right atrial appendage directly into the left atrium and the right atrium was completely excluded. Great care had been taken posteriorly to preserve sufficient of this chamber to maintain an adequate passage for superior caval inflow.

The finger was now removed from the appendage and the base was tied off and then oversewn. The pericardium was closed except for a 2.5 cm. portion at each end of the incision. A pleural drain was placed through a thoracic stab incision and the chest closed.

*Comment:* Several important questions presented themselves when it was determined to attempt this procedure, so feasible in the dead heart, on a living patient. Inasmuch as the defect so often, in the course of time, gives rise to cardiac arrhythmias, would the necessary manipulation of the atrium and the trauma to its wall engender severe disturbances of rhythm? In this case, at least, a satisfactory answer was forthcoming. During the entire

procedure the heart behaved admirably. Blood pressure was maintained satisfactorily and at no time was the operator or the anesthesiologist given cause for concern over the patient's condition. Atrial fibrillation developed on the second postoperative day but rhythm reverted to sinus type spontaneously after one week.

Although obliteration of the defect in the dead heart seemed to allow sufficient room for venous return, would this situation exist under dynamic conditions? This question, too, was answered satisfactorily in this single case. Following completion of the procedure, although the size of the right atrium had been greatly reduced, there was an adequate lumen to receive venous inflow. Indeed, the capacity of the chamber was now perhaps only slightly smaller than normal (figure 11).

Blalock<sup>26</sup> has stated that pulmonary hypertension might be a contraindication to closure of an atrial septal defect, depending on whether the hypertension is primary or secondary and, if secondary, whether it is reversible. In the presence of marked pulmonary arteriolar disease, right atrial pressure may rise. He envisioned closure of the defect as possibly removing a safety valve for preventing excessive increase in right atrial pressure and transforming the condition into one resembling Ayerza's disease. We did not believe that the pulmonary vascular changes and the hypertension are primary and irreversible, and felt that the hypertension would be relieved, in part at least, immediately upon closing the defect. We were pleased that this was borne out by cardiac catheterization three weeks postoperatively. The mean pulmonary arterial pressure had fallen from 65 to 40, and the mean right ventricular pressure from 55 to 40. No doubt with the passage of time there will be further reduction in pressure as the pulmonary vascular changes regress.

It will be noted in the table that the arterial oxygen saturation at the time of the postoperative cardiac catheterization was only 82.4 per cent, whereas preoperatively it had been 94 per cent. We do not believe that this indicates that a right-to-left shunt had been initiated through an unsuspected defect. Rather, we believe that the postoperative retention of bronchial secretions and the ensuing pulmonary pathology were responsible for inadequate aeration and oxygenation. At no time was there cyanosis, and polycythemia did not develop. At the present time, three months postoperatively, the patient has no symptoms referable to her heart and no evidence of the presence of a right-to-left shunt. Her arterial oxygen saturation recently determined by Dr. Bernard Brofman of Cleveland was 95 per cent.

#### SUMMARY AND CONCLUSIONS

1. The embryologic, physiologic and clinical features of interatrial septal communications have been reviewed, with particular emphasis on the uncomplicated defect.

2. Patent foramen ovale, uncomplicated by other lesions, is of little significance physiologically.

3. Atrial septal defects usually give rise to a left-to-right shunt. Pulmonary hypertension, right heart strain and eventual cardiac failure often result.

4. Atrial septal defects, according to their natural histories, may be lethal in infancy, may allow survival to childhood or adolescence, may be compatible with life only to early adult or middle years or, rarely, with a full span of life. Often the symptoms are so severe that a prolonged life is a burden.

5. The relatively poor prognosis for life and comfort and the inadequacy of medical treatment to halt progression of the disease justify surgical intervention to eliminate the shunt.

6. Several laboratory and a number of clinical approaches to surgical correction have been reported. Each has serious deficiencies.

7. The ideal surgical technic should be one which allows obliteration of the defect without compromising atrial flow, which does not necessitate the introduction of a prosthetic device, and which can be accomplished with dispatch.

8. A technic termed atrio-septo-pexy was conceived and shown to be feasible in an autopsy specimen. It involves suturing the right atrial wall to the margin of the defect, aided by a finger placed in the right atrium through the appendage.

9. Clinical application of the technic in one patient resulted in complete obliteration of the shunt and complete relief of symptoms. This is believed to be the first case of atrial septal defects to be completely closed by surgical means without introduction of a prosthesis.

10. We believe this to be the first example of true intracardiac suturing for relief of a cardiac defect.

#### ADDENDUM

This operation has since been done in five additional cases, with three very satisfactory results but, unfortunately, with two operative deaths, both in cases of very advanced disease.

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## DIETARY MODIFICATION OF THE METABOLIC AND CLINICAL EFFECTS OF ACTH AND CORTISONE \*

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THE accumulation of knowledge and the development of concepts regarding the place of ACTH and cortisone in clinical medicine have followed an interesting pattern during the past three years. The first period might be termed the *phase of incredulity*. This persisted a relatively short time. The second phase would be dubbed properly the *era of extreme euphoria*. The third period is now with us. Its most outstanding characteristic is the *alarm reaction*.

Such a pattern has been followed in the case of many therapeutic agents. In a measure it bears out the physiologic axiom that for every action there is an equal and opposite reaction. In the case of ACTH and cortisone, both swings of the pendulum have been of excessive amplitude.

The data and concepts which are presented in this paper will, it is hoped, help to initiate the fourth phase, or *phase of maturity and stability*. Before presenting the data, a small amount of chronologic reminiscence may be in order.

1. In the spring of 1949 it was demonstrated that ACTH and cortisone were capable of completely eradicating the signs and symptoms of active rheumatoid arthritis.

2. During the subsequent months it was demonstrated further that these hormones would eradicate the signs and symptoms of a bewildering variety of disease states, most of them of unknown etiology.

3. In the autumn of 1949, and in subsequent months, it was shown that the administration of ACTH or cortisone to patients with a variety of infections of known etiology resulted in disappearance of the signs and symp-

\* Presented at the Thirty-third Annual Session of the American College of Physicians, Cleveland, Ohio, April 24, 1952.

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Grateful acknowledgment is made to the Armour Laboratories for supplies of ACTH used in these studies; to Merck & Company for supplies of cortisone, and to Mead Johnson for supplies of Lonalac and Casec.

This work has been supported in part by grants from the National Institutes of Health and from the Armour Laboratories.

§ With the technical assistance of FLORENCE OLSON, ELEANOR KIPP, NANCY DAWSON and MARJORIE COELHO, Oakland, California.



toms of the disease, but that no inhibition of growth of the causative organism was produced.

4. It was soon recognized that in the majority of chronic disease states in which the hormones were effective, prolonged administration was essential if remission was to be maintained.

5. Also, it became apparent that prolonged administration resulted in the appearance of a variety of undesirable effects, up to and including the production of Cushing's syndrome. In some instances the untoward effects were so severe as to necessitate discontinuance of medication.

Many of the reports on which the foregoing statements are based are reviewed in a previous paper from this laboratory.<sup>1</sup> These observations have raised many questions, among them:

1. Are the untoward effects controllable or preventable in whole or in part?
2. Does one have any reason to believe that medication can eventually be discontinued in any significant number of patients with chronic disease states?
3. In chronic conditions such as rheumatoid arthritis, after two to three years' treatment, is the average patient apt to be much better than if he had been treated with aspirin?

We shall attempt to supply some answers to these questions in reverse order. Most of the answers will be based upon our own experience during the past three years. Specific data will be considered in the answer to the first question.

In our experience, the answer to question number three is an unequivocal yes. More than 50 per cent of our rheumatoid patients who have been treated for more than two years have been returned to full activity. Amplification of this statement will be contained in a later paper.

In answer to question 2, as yet we have been unable to discontinue completely medication in any patient with rheumatoid arthritis. The majority of patients who have been followed for periods of more than 18 months, however, are well maintained on quite small dosage of hormones (in some instances as little as two to four units of ACTH or 25 mg. of cortisone daily).

In an attempt to answer question 1, it will be well to list the undesirable clinical effects which have been reported, and to attempt to correlate them with known metabolic effects:

#### *Untoward Clinical Effects*

1. Edema and hypertension.
2. Masking of symptoms and signs of infection.
3. Decreased localization of infectious processes.
4. Diabetogenesis.
5. Perforation of gastrointestinal ulcerations.

6. Precipitation of psychoses.
7. Muscle weakness.
8. Osteoporosis.
9. Hirsutism.
10. Loss of head hair.
11. Acne.
12. Pigmentation.
13. Actual Cushing's syndrome.
14. Impaired wound healing.

#### *Undesirable Metabolic Effects*

1. Protein catabolism.
2.  $\text{Na}^+$  and water retention.
3.  $\text{K}^+$  loss.
4. Derangement of carbohydrate metabolism.
5.  $\text{Ca}^{++}$  and  $\text{PO}_4^{---}$  depletion.
6. Depletion of other essential constituents of protoplasm.

In the light of present knowledge, one may attempt to correlate metabolic and clinical effects as follows:

1. *Protein hypercatabolism (or antianabolism).*
  - a. Ulcer penetration and perforation.
  - b. Impaired wound healing.
  - c. Diminished localization of infection.
  - d. Muscle weakness.
  - e. Osteoporosis.
  - f. Diabetogenesis.
2. *Sodium retention.*
  - a. Edema.
  - b. Hypertension.
  - c. Mental derangement (?).
3. *Potassium depletion.*
  - a. Muscle weakness.
  - b. Insulin resistance (?).
  - c. Mental derangement (?).

Such correlation suggests that some of the undesirable clinical effects can be favorably modified or prevented by appropriate dietary supplementation or limitation as well as by certain other measures, viz.:

1. Edema and hypertension may be largely or entirely prevented by restriction of sodium. In some instances it may be necessary to restrict the

intake to less than 100 mg. daily, and not infrequently to amounts of less than 300 mg.\*

2. Muscle weakness can frequently be modified or prevented by adequate potassium supplementation. It may be necessary at times to administer as much as 20 gm. of potassium chloride a day. It is possible, although by no means proved, that such potassium supplementation may also lessen the tendency to development of psychoses, and may lessen the tendency to edema formation in the presence of moderate sodium intake. Recent observations in our laboratory also suggest that potassium supplementation may lessen the tendency to development of insulin resistance in diabetic patients to whom ACTH and cortisone are administered.

3. The tendency to impaired wound healing and to perforation of gastrointestinal ulceration probably is attributable in part to the protein catabolic (or antianabolic) effects of ACTH and cortisone. Whether the administration of huge amounts of protein to patients with known or probable gastrointestinal ulcerative processes will prevent this hazard is still to be demonstrated. Such patients should also receive prophylactic antacid, antispasmodic therapy in a vigorous fashion!

4. Since the resistance to infection and the ability to localize infections are in no small measure products of protein anabolic processes, in this connection also the need for intensive protein supplementation is apparent. Much additional information will be required, however, before one can state with any assurance that such supplementation will prevent the tendency of ACTH and cortisone under some circumstances to predispose to dissemination of infection. Adequate antibiotic therapy is mandatory in all patients receiving ACTH-cortisone therapy in whom infection is an actual or a potential problem.

5. Since osteoporosis is thought to be a disease characterized by impaired bone matrix formation, the administration of large amounts of protein would be mandatory from both a prophylactic and therapeutic standpoint. Also, the use of hormones, such as testosterone, which selectively stimulate protein anabolism may lessen or eliminate the tendency to such skeletal abnormality. If and when a pituitary growth factor which is effective in the human subject is available, this may also be of value in this regard.<sup>2</sup> Further, although osteoporosis is not primarily a disease of disturbed calcium and phosphorus metabolism, the administration of adequate amounts of these minerals as well as of vitamin D is in order in view of the net depletion which tends to result from prolonged ACTH and cortisone administration.

6. A complete explanation of the diabetogenic effects of ACTH and cortisone is not yet available. At least three possible mechanisms are involved, namely, acceleration of neoglucogenesis from protein; acceleration of neoglucogenesis from fat, and the production of "insulin resistance." What-

\*The use of desalted milk or of desalted calcium caseinate may be necessary to achieve a high protein-low sodium intake.

ever the mechanisms, limitation of carbohydrate intake in patients receiving ACTH and cortisone seems physiologically sound.

#### EXPERIMENTAL OBSERVATIONS

In the course of studies dealing with the effects of ACTH and cortisone steroids upon lipid metabolism, we have had occasion to maintain patients on formula diets containing only fat, fat plus protein, and fat plus protein plus carbohydrate in varying ratios. All diets were supplemented with essential electrolytes and vitamins. It was observed that the first patient (a rheumatoid arthritic) maintained on a pure fat diet behaved in a somewhat unexpected fashion clinically and metabolically (figure 1), viz.:

1. Her urinary 17-ketosteroid excretion was one-half to one-third the value expected during the administration of large amounts of ACTH and of ACTH plus testosterone.
2. Despite the administration of huge amounts of ACTH and cortisone, with the resultant production of a complete remission of her rheumatoid arthritis, she developed no untoward clinical manifestations during hormonal therapy.
3. Cushingoid manifestations appeared as soon as she received a mixed diet, even though the diet was low in sodium and high in potassium.

With this observation in mind, a second rheumatoid patient was studied on a variety of formula diets. This man had previously received prolonged ACTH therapy, and had become resistant to ACTH in terms of benefit to his joints. In addition, he manifested many of the untoward clinical effects.

It will be noted in figure 2 that administration to this patient of a pure fat, and subsequently of a high fat, relatively low protein diet, in conjunction with very large dosage of ACTH, resulted in a 17-ketosteroid excretion which averaged less than 10 mg. per 24 hours. Despite this he had marked improvement in his disease, and at the same time a progressive disappearance of Cushingoid manifestations. The addition of large amounts of protein to the diet resulted in a significant increase in 17-ketosteroid excretion, continued improvement of his disease and no return of untoward clinical manifestations. Addition of increasing amounts of carbohydrate to the diet was associated with a progressive rise in 17-ketosteroid excretion, and was also associated with reappearance of Cushingoid manifestations. The dose of ACTH was kept constant throughout the study except as indicated in figure 2.

From these studies there seems little question that the production and/or metabolism of adrenal steroids is modified in a rather major way by dietary composition. Other patients are at present undergoing similar studies on the metabolic ward to determine the constancy and the significance of this type of modification of hormonal effects.

Also, over the past several months a group of 14 patients suffering from rheumatoid arthritis and from other disease states has been followed under



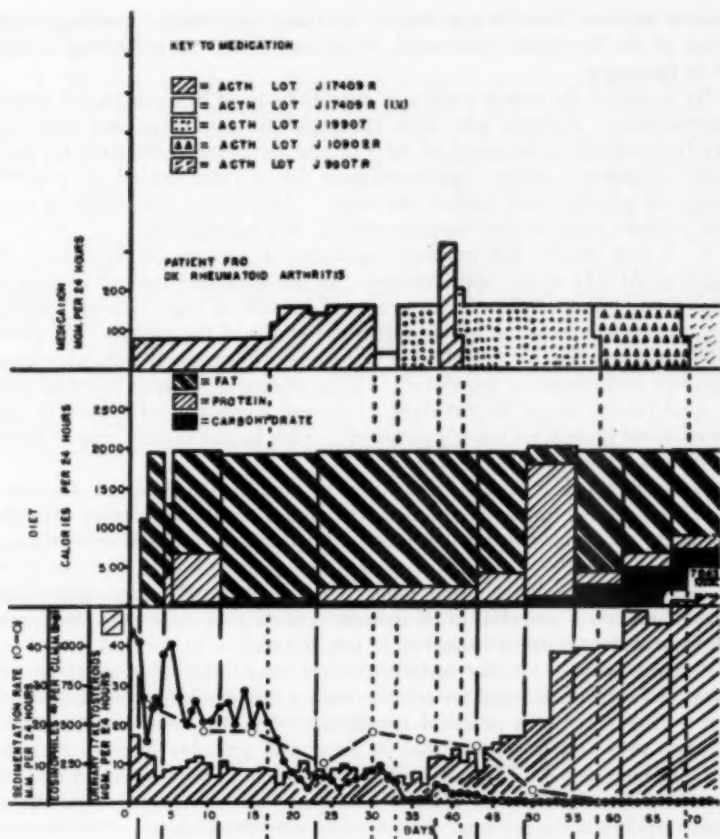


FIG. 2. The effect of diet on metabolic effects of ACTH. There was a sevenfold increase in 17-ketosteroid excretion on a high carbohydrate diet as compared to a very high fat diet.

semicontrolled conditions on the general wards. The plan has been to maintain them on constant dosage of ACTH and/or cortisone, and to observe the changes (if any) in clinical response and in eosinophil and sedimentation rate response on different dietary regimens. The impressions from such observations to date are as follows:

1. *Sodium limitation* is indicated in essentially all patients receiving ACTH or cortisone. The degree of limitation will depend upon the individual and upon the dosage being used. It is well to regard 1 gm. of sodium per day as the upper limit of tolerance in patients receiving intramuscular ACTH Gel in amounts in excess of 10 mg. daily, or cortisone in

amounts of more than 50 mg. daily. In many individuals receiving large dosage of the hormones, restriction of sodium to less than 300 mg. a day will be necessary.

As is always the case in medicine, exceptions must be made to any broad generalization. Patients who have the nephrotic syndrome, and who are actively diuresing as the result of ACTH and cortisone administration, may require intensive sodium supplementation for a brief period to prevent severe and possibly fatal sodium depletion. Also, under conditions of systemic acidosis some sodium supplementation may be required.

2. *A high protein diet* is always necessary in patients on short-term or long-term ACTH or cortisone therapy. In the adult this amount of protein varies from 120 to 200 or more grams of protein of high biologic quality daily, depending upon the initial nutritional status of the patient. In those individuals in whom oral feeding is impossible, intravenous administration of protein hydrolysate is mandatory. It is, of course, equally essential that the total caloric intake be sufficient to prevent excessive catabolism of the administered protein for energy purposes. This is particularly true in those individuals whose nutrition is poor.

Again to consider possible exceptions to broad generalizations, the matter of high protein intake in a patient with major renal insufficiency presents a difficult problem. In few of these individuals is ACTH or cortisone indicated.

3. Excepting only the individual with renal insufficiency, *potassium supplementation* is essential in all patients treated with ACTH or cortisone. Our present dose range is from 4 to 12 gm. per day.

4. Only patients on the metabolic ward have been maintained on fat alone. In view of the need for protein, such a diet would be contraindicated even if feasible from a practical standpoint. On the basis of clinical observation thus far, it appears that in some and probably in most patients receiving intensive ACTH-cortisone therapy, diets in which protein and fat represent the sole source of calories are compatible with a maximal therapeutic response and a minimal occurrence of untoward effects. Substitution of carbohydrate for a large portion of dietary fat may reverse this ratio. It is still to be established whether there is a critical level of carbohydrate ingestion, or whether a high level of dietary fat per se is desirable.

In addition to the factors which have been considered, it is probable that other constituents of protoplasm may be seriously depleted during ACTH-cortisone therapy. This matter is receiving careful study in the metabolic ward at the present time. It is hoped that information obtained in such studies will increase the therapeutic usefulness of these hormones.

#### DISCUSSION

The phase of extreme euphoria in regard to the use of ACTH and cortisone is definitely and properly past. Lest the pendulum swing too far in



the opposite direction, however, it is important to recall the following quite unequivocal facts:

1. Many thousands of patients with a wide variety of disease states are living, and in many instances are in excellent health, who without ACTH or cortisone almost certainly would be dead. In this category, to name a few, are patients with pemphigus, lupus erythematosus and dermatomyositis.

2. Many patients are productively active who had been in semi-invalid or fully invalid status for many years. This applies particularly to patients with rheumatoid arthritis and severe asthma. The majority of such patients, prior to the advent of ACTH and cortisone, had received the full gamut of available therapy, despite which their course was progressively downward.

3. The majority of valuable pharmaceuticals are capable of producing harmful effects. This is very true in the case of ACTH and cortisone. The purpose of this report is to indicate that specific dietary (and other) measures can minimize many of the untoward effects and hence, at least in a relative sense, increase the therapeutic value of the hormones.

#### SUMMARY

The development of untoward clinical and metabolic effects in patients receiving ACTH and cortisone may seriously interfere with their therapeutic application. Specific dietary modification may lessen or prevent the development of some of these untoward effects. The major considerations in the construction of an "ACTH-cortisone diet" are high protein, adequate calories, low carbohydrate, low sodium, high potassium. It is probable that other dietary factors will also be found to be of importance in determination of the net effects of these hormonal agents.

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## ADDISON'S DISEASE SECONDARY TO METASTATIC CARCINOMA OF THE ADRENAL GLANDS \*

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SINCE Addison's classic and comprehensive description of the disease bearing his name,<sup>1,2</sup> accepted etiologic factors have included tuberculosis and cytotoxic contracted adrenals (atrophy) almost exclusively. Much less frequently, the disease has been ascribed to amyloidosis, fatty degeneration, syphilis, tumors, vascular lesions and trauma of the adrenals. Both glands are involved completely and extensively in almost all cases, although rare cases with unilateral destruction or aplasia have been reported.<sup>3</sup>

A complete review of the literature reflects the widespread doubt cast on the mechanism of neoplastic destruction of the adrenals, more specifically by metastatic involvement, as a cause of adrenal cortical insufficiency of a degree severe enough to be accepted as Addison's disease. Thomas Addison proposed this basis in four admittedly unconvincing cases in his first series of 11 cases,<sup>1,2</sup> but since that time reports of Addison's disease produced by metastatic neoplastic destruction of the adrenals have been distinctly rare, and include only seven cases in the modern literature of the past 50 years. Guttman,<sup>3</sup> in a review of 566 cases during the years 1908-1930, found only five cases of neoplastic disease, three of which were ascribed to metastatic disease of the adrenals. In 1933, Poynton and co-authors<sup>4</sup> reported two cases of clinically suspected Addison's disease, both due to metastases from bronchogenic carcinoma. The first case seemed classic, and the diagnosis was confirmed by postmortem evidence of bilateral replacement of adrenal tissue; the second case, however, lacked the usual clinical features of the disease, and at autopsy only one gland was replaced by tumor. Aguilar and Bancalasi<sup>5</sup> in 1940 reported a case of Addison's disease secondary to adrenal destruction by metastatic disease from a bronchogenic carcinoma, and in 1941 Madheim<sup>6</sup> reported another case due to adrenal metastases from a gastric carcinoma. Strang<sup>7</sup> reported a case which at first was thought to be characteristic of primary Addison's disease. During subsequent hospitalization, pulmonary lesions were found which, at autopsy, proved to be bronchogenic carcinoma. Bilateral adrenal replacement by metastatic tumor, the exact extent of which was not described, was also present. To the best of our knowledge, no further reports have appeared since Strang's case in 1942. Rowntree and Snell<sup>8</sup> failed to find a single

\* Received for publication July 13, 1951.

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instance of carcinomatous etiology in more than a hundred cases of Addison's disease; and in 70 cases of metastases to one or both adrenals, clinical adrenal cortical insufficiency was absent in all. Similar findings prevail in the literature<sup>9,10</sup>; in all reports the rarity of metastatic tumor as a cause of Addison's disease is apparent. Although bilateral metastases to the adrenals are admittedly frequent and often extensive, Soffer<sup>11</sup> alleges that they are rarely destructive and extensive enough to produce the characteristic picture of Addison's disease.

It is our purpose to present three proved instances, plus a possible fourth, of Addison's disease secondary to destruction of the adrenals by metastatic tumor, implying thereby that such sequence is not so rare as the literature would indicate. It is also our feeling that the diagnosis is missed frequently because of the resemblance of the advanced state of malignant disease to the clinical picture of Addison's disease. Unless symptoms of increased pigmentation, cachexia, weight loss, asthenia, hypotension and cramplike pains are investigated for adrenal cortical hypofunction by electrolyte, endocrine and carbohydrate tolerance studies, it is apparent that the presence of a malignancy might be invoked to explain the whole picture.

#### CASE REPORTS

*Case 1.* A 58 year old white male was admitted to Queens General Hospital on October 15, 1948, because of increasing weakness, anorexia and weight loss. The patient claimed good health until approximately one year prior to admission, when he first noted vague indigestion and anorexia, at which time a diagnosis of "nervous stomach" was made. Six months before admission he developed pain in the low back. The pain persisted, with increasing severity until admission. Three months prior to admission a physician noted the presence of a right inguinal mass, and at that time a chest plate was said to show a right hilar mass. The inguinal mass was biopsied and the reported histology was that of "adenocarcinoma, the primary site undetermined, possibly gastrointestinal tract, bronchus or prostate." He received a course of Pteropterin and irradiation to the chest, but despite such treatment his extreme asthenia, back pain and anorexia persisted. He had lost 40 pounds in the year prior to admission.

Physical examination on admission revealed a well developed, emaciated, asthenic 58 year old white male who appeared chronically ill. Temperature, 98.6° F.; pulse, 80 per minute; respirations, 16 per minute; blood pressure, 110/80 mm. of Hg. He was pale and sallow; there were numerous deeply pigmented spots on the face, arms, chest and back, which the patient claimed had always been present. The mucous membranes were pale but free of pigmentation. There was no increased pigmentation in the axillary folds or at pressure points. Hair was present in normal distribution, and postradiation pigmentation was present over the right anterior chest wall. Aside from an inguinal scar with underlying stony hard nodules and an apparently immobile right diaphragm, the remainder of the physical examination was unremarkable.

Laboratory tests on admission were as follows: red blood cells, 3.12 M.; hemoglobin, 9.5 gm.; white blood cells, 11,250, with 79 per cent polymorphonuclears. Routine urine examination excluded albuminuria and glycosuria; microscopy revealed no formed elements; specific gravity was 1.016. Fasting blood sugar, 90 mg. per cent; blood urea nitrogen, 20 mg. per cent; blood chlorides, 96 mEq./L., serum inorganic

phosphorus, 5.3 mg. per cent; acid phosphatase, 0.8 unit; alkaline phosphatase, 11.7 King-Armstrong units; icterus index, 4; total protein, 6.8 gm. per cent, with a normal albumin-to-globulin ratio. Chest x-ray revealed a homogeneous area of absent illumination involving the upper portion of the right lung field and extending down to the second rib anteriorly. This suggested partial atelectasis of the right upper lobe which, in turn, suggested the presence of a primary endobronchial carcinoma. There was no evidence of rib destruction, and complete bone survey showed no metastatic disease. A flat plate of the abdomen was not remarkable. An electrocardiogram was within normal limits.

*Course in Hospital:* At first the patient suffered from severe, intractable pain, for which considerable narcotic therapy was required. Because of this severe pain a differential alcohol spinal block was performed, which resulted in complete relief of pain, complicated, however, by a cord bladder. After one month of hospitalization, definitely increasing generalized pigmentation was noted, especially at pressure points and in the buccal mucosa. The patient's asthenia became worse, the blood pressure fell to 80/60 mm. of Hg, and mild diarrhea developed. Laboratory work at this time revealed a mild anemia, blood chlorides of 85 mEq./L., blood sugar of 65 mg. per cent, serum sodium of 122.5 mEq./L., serum potassium of 20.5 mg. per cent (normal, 15 to 20 mg. per cent), and a blood urea nitrogen of 20 mg. per cent. A Robinson-Power-Kepler water test was performed, with positive results in both parts I and II; the "A" factor in Part II equaled 5.7 (normal, greater than 30).<sup>12</sup> Urinary 17-ketosteroid excretion was 4.34 mg. in 24 hours (normal, 11 to 20; average, 15).<sup>\*</sup> The laboratory findings and the clinical picture at this time suggested the presence of Addison's disease, and it was felt that the etiology was bilateral adrenal destruction from metastasizing bronchogenic carcinoma. The patient was placed on desoxycorticosterone acetate, 5 mg. intramuscularly every other day, and 5 gm. of supplemental sodium chloride daily. On this regimen, the blood pressure returned to normal level, the diarrhea subsided and the patient's appetite improved. He gained 10 pounds, and there was both subjective and objective evidence of increasing strength. Blood chlorides increased to 101 mEq./L. However, three weeks after the institution of therapy, and following two and one-half months of hospitalization, the patient lapsed into coma and died.

The autopsy (performed by Dr. H. Steinberg) revealed the following: The right upper lobe bronchus was stenosed by firm, white, tumor tissue which completely encircled the lumen. The peripheral portion of the right upper lobe was the site of a firm, yellowish-gray process of consolidation. Grossly, the tumor in the chest seemed to be limited to the right upper lobe bronchus. Gross metastatic involvement of the jejunum, of multiple subcutaneous lymph nodes and of both adrenal glands was seen; the latter were completely replaced by firm, white tumor tissue. Small scattered islands of yellow material could be seen scattered throughout both glands. Microscopically, the primary endobronchial tumor (figure 1) was seen to be predominantly adenocarcinoma, as were all the metastatic areas. Microscopic examination of the adrenals (figure 2) revealed complete replacement of glandular structure by tumor with hyalinosis and fibrosis. The yellow islands seen in the gross were noted to be necrotic tumor tissue.

*Case 2.* A 73 year old white male grave-digger was admitted to the Queens General Hospital because of a severe "chest cold." The patient had been well until seven months before entry, when he noticed the insidious onset of a dry cough which gradually became productive of moderate amounts of a mucopurulent sputum. For

\* Modification of the method of Callow and Callow as performed in the biochemical laboratory of the Jewish Hospital of Brooklyn through the courtesy of Dr. Charles S. Byron. All other 17-ketosteroid determinations reported in this paper were performed in the same laboratory.

about four months there had been increasing exertional dyspnea and orthopnea. Only slight, intermittent ankle edema was noticed. The patient had lost 20 to 30 pounds in weight over the seven month period. Anorexia and nausea were prominent, but no vomiting or diarrhea had occurred. Associated with his wasting was progressive and marked generalized weakness. On the day of admission, the patient developed slight swelling of the face and forearms.

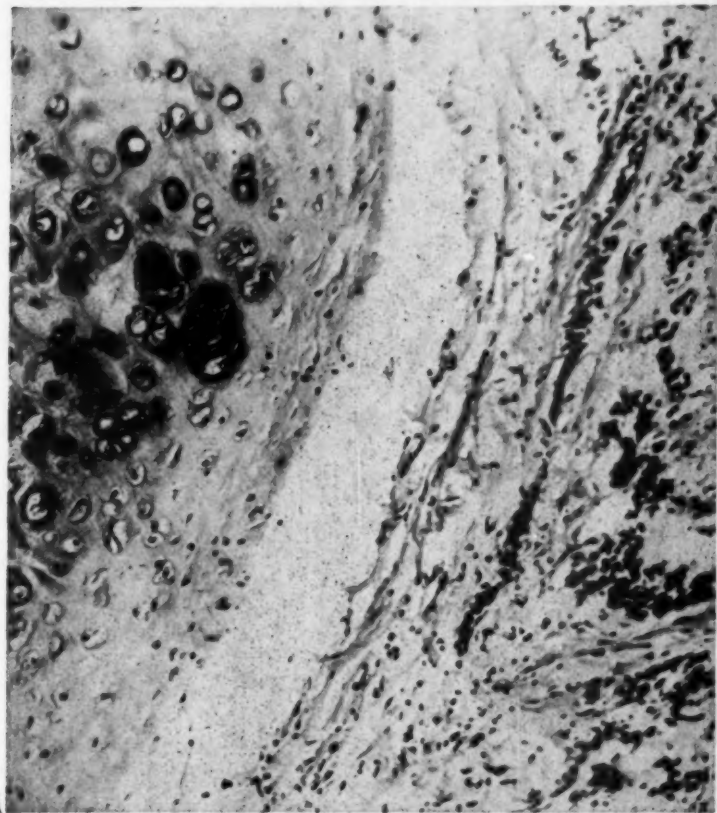


FIG. 1. Section through primary site in right upper lobe bronchus of case 1 revealing endobronchial adenocarcinoma invading the submucosa.  $\times 720$ .

Physical examination revealed an elderly, emaciated white male who appeared acutely and chronically ill. He was moderately orthopneic and cyanotic. Frequent coughing paroxysms appeared to be exhausting to the patient. He was obviously very weak, and examination was difficult. The temperature was  $99^{\circ}$  per rectum. The skin was dry, cool and diffusely bronze-colored. The skin folds were pigmented brown. Several black freckles were noted on the face and upper extremities. There

was a suggestion of facial edema. The eyes were sunken and soft. Several small irregular areas of bluish-brown pigmentation were evident on the buccal mucosa. Fullness in both supraclavicular fossae and distention of the neck veins were conspicuous. The trachea was displaced to the right. Chest examination revealed dullness, absent tactile fremitus and markedly diminished breath sounds in the region

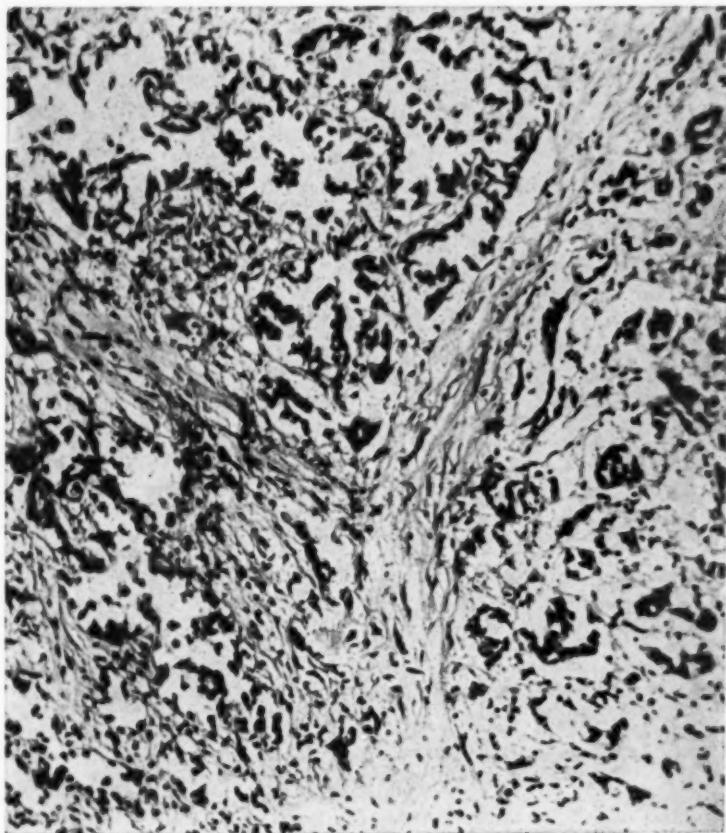


FIG. 2. Section through adrenal gland of case 1, revealing complete obliteration of normal architecture and elements by metastatic adenocarcinoma.  $\times 720$ .

of the right base. No râles were heard. The heart was not enlarged. Heart sounds were distant. The blood pressure was 100/60 mm. of Hg. The abdomen was scaphoid, soft and nontender. No organs or masses were palpable. There was moderate edema of both upper extremities. Slight clubbing of the fingers and toes was present. The pulse was slow, regular and somewhat feeble. The remainder of



the physical examination was negative. A presumptive clinical diagnosis of Addison's disease secondary to bilateral adrenal metastases was made. Superior vena caval obstruction was also thought to be present.

Pertinent laboratory data were: hemoglobin, 8.5 gm.; red blood cell count, 3.3 million. Routine urinary examination was negative. Blood urea nitrogen was 15 mg. per cent; serum chloride, 99 mEq./L., and fasting blood sugar, 65 mg. per cent. Part I of the Robinson-Power-Kepler water test was positive. There was a total 24 hour urinary excretion of 17-ketosteroids of 8.5 mg. X-ray of the chest revealed atelectasis of the right lower lobe, with enlarged right tracheobronchial lymph nodes. On bronchoscopy, a firm, stenosing, superficially necrotic mass was visualized in the right main-stem bronchus.

The patient's course was progressively downward. Treatment consisted of irradiation to the mediastinum, penicillin administration and infusions of glucose and saline. His profound weakness was striking. Apathy was marked, his speech grew weaker and the pigmentation became more intense. Blood pressure ranged between 90 and 70 systolic. Daily temperatures averaged 98° per rectum. Wasting was rapid, and the patient died eight weeks after admission.

*Relevant Autopsy Findings* (courtesy of Dr. W. Victor): The right main stem bronchus contained an incompletely obstructing intrinsic mass of tumor tissue, which was firm and grayish-white on cut section. The peripheral portions of the lung, particularly the right middle and lower lobes, were the site of a chronic, suppurative bronchiectatic process. Metastatic tumor was seen to be present in the right visceral pleura, in the liver and in both adrenal glands, which measured 12 by 8 by 4 cm. (left), and 8 by 5 by 2 cm. (right). Both glands were apparently completely replaced by firm, grayish-white tumor tissue in the gross. Multiple cut sections failed to reveal intact adrenal tissue. Microscopy revealed the endobronchial tumor, as well as all metastases, to be squamous cell carcinoma. Multiple sections of both adrenal glands revealed only small, scattered areas of fasciculata that could be identified microscopically as intact adrenal tissue (figure 3). The remaining portions of both glands were replaced by tumor.

*Case 3.* A 47 year old white male was admitted to the Queens General Hospital with a history of good health until approximately 10 to 12 weeks prior to admission, when a moderately productive, unrelenting cough, exertional dyspnea, anorexia, weight loss and abdominal pain were noted. The patient's past history was non-contributory. Tuberculous contact and exposure were denied.

On physical examination the patient was seen to be a well oriented, debilitated 47 year old white male. He had a diffuse "tanning" pigmentation of his skin. He was troubled by intermittent cough and abdominal pain. Temperature, 101° F.; blood pressure, 100/70 mm. of Hg. Dyspnea and dehydration were apparent, and there was evidence of weight loss. The buccal mucosa revealed a patchy distribution of gray-brown pigment; no pigmentation was seen in the umbilicus, scars, anogenital region, pressure points or creases of the hands. The heart was not enlarged. Heart sounds were of fair intensity. The lung fields were negative on physical examination, and the liver was enlarged to five fingerbreadths below the costal margin on inspiration. X-rays revealed an oval, sharply demarcated shadow arising in the left hilar region; the interpretation was bronchogenic cancer. The clinical impression was that of bronchogenic carcinoma, with adrenal cortical insufficiency due to metastases to both adrenal glands. The urinalysis was negative; hemoglobin varied between 8.6 and 9.7 gm. The white blood count ranged between 11,000 and 17,000, with 80 to 90 per cent polymorphoneutrophils. Blood chlorides were 88 mEq./L.; serum sodium was 116 mEq./L.; serum potassium was 6.2 mEq./L. (normal, 3 to 5); 17-ketosteroid excretion was 5.0 mg. in 24 hours. Robinson-Power-Kepler water tolerance test was positive in both parts I and II; the "A" factor calculated to 11.



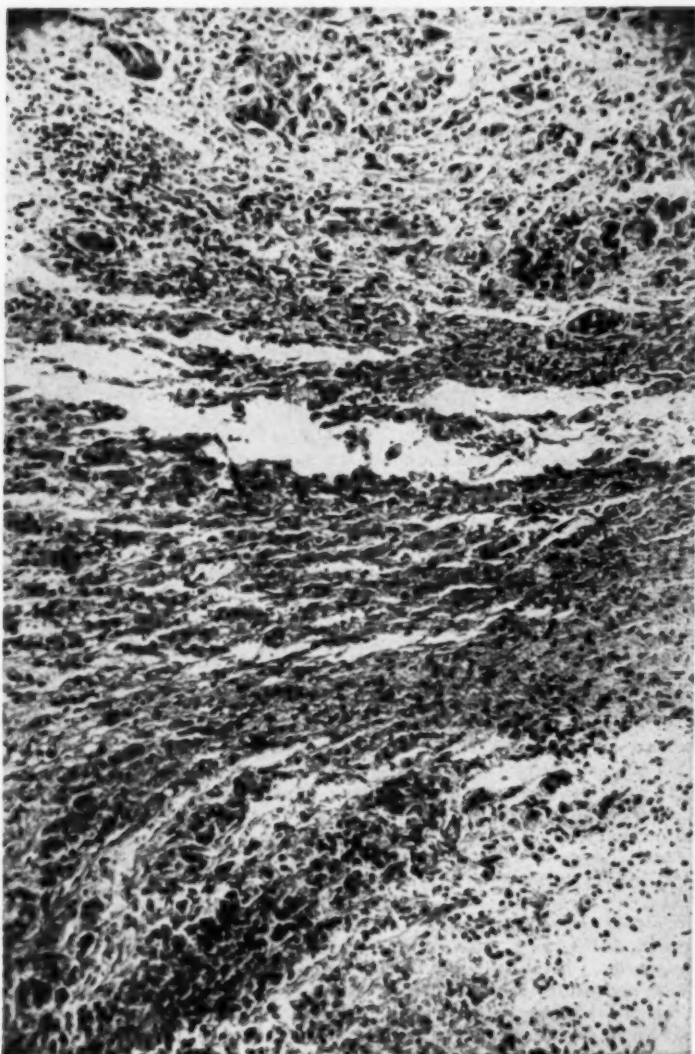


FIG. 3. Section through adrenal gland of case 2, revealing remnant of intact fasciculated surrounded by metastatic squamous cell carcinoma.  $\times 260$ .

Fasting blood sugar was 114 mg. per cent, and blood urea nitrogen varied between 8 and 11 mg. per cent on repeated examinations.

The patient developed signs of consolidation in the left lower lung field. Blood pressure dropped to 95/60 mm. of Hg, despite the administration of desoxycorticosterone acetate. The patient complained of thirst and intermittent vomiting, and died on March 3, 1950. Antemortem Silverman needle biopsy of the liver revealed cirrhotic changes without metastases. Autopsy consent could not be obtained.

*Comment:* Unfortunately, permission for an autopsy was denied. However, the clinical diagnosis was borne out by the Robinson-Power-Kepler test, serum sodium and potassium changes and the 17-ketosteroid excretion studies. This case illustrates a rapidly developing cachexia associated with the development of adrenal cortical insufficiency in a case of bronchogenic cancer, in which the primary lesion was rather small in size and the liver free of detectable metastases.

*Case 4.* A fourth case, seen in the same period, is not reported as a proved case because of lack of laboratory confirmation. However, this 52 year old white male had suffered for one year with a weight-losing gastrointestinal condition. He was admitted in a cachectic state and found to have generalized pigmentation as well as characteristic buccal pigmentation, asthenia, nausea, vomiting and hypotension. Only Part I of the Robinson-Power-Kepler water test was completed before death, and it was positive. The diagnosis of Addison's disease was proposed on clinical grounds. At autopsy (performed by Dr. J. Wallach), both adrenals were extensively infiltrated by tumor tissue, metastatic from a primary gastric carcinoma. Microscopy revealed moderate amounts of intact adrenal cortical tissue, interrupted by islands of metastatic carcinoma and fresh cortical hemorrhage.

#### DISCUSSION

In the light of the numerous reports of Addison's disease, in which the etiology is given almost exclusively as either tuberculosis or idiopathic atrophy, it is remarkable that three proved cases (and a probable fourth) of Addison's disease due to metastatic destruction of the adrenals have been collected from one hospital in a short two-year period. This becomes the more striking when compared with a review of 50 years of literature, in which only seven such cases were uncovered, and during which time several authors insisted that such cases are very rare.

These cases suggest a greater etiologic incidence of adrenal metastatic carcinoma in the production of Addison's disease than is usually accepted. This observation is perhaps not so remarkable in view of the much higher incidence of metastatic adrenal disease found at autopsy in recent years as a corollary to the increasing frequency of bronchogenic carcinoma.

It should be noted, however, that extensive metastatic destruction of both adrenal cortices often does not produce this syndrome,<sup>8, 11</sup> a circumstance that has been noted also in tuberculous involvement of the adrenals. Guttman<sup>8</sup> found that, of 34 cases of bilateral tuberculous adrenal destruction, of comparable extent in each case, six failed to develop the clinical picture of Addison's disease.

It is our impression that Addison's disease is produced more frequently by metastatic tumor of the adrenals than is generally recognized, but the symptomatology which ordinarily might prompt confirmatory laboratory investigation is usually attributed to the generalized cachexia which accompanies malignant disease. We have noted in patients with bronchogenic carcinoma, however, a contrast between the group of patients without adrenal involvement and those with adrenal insufficiency due to metastatic disease. It has been our impression that the former group with a corresponding degree of metastatic disease is usually better preserved when first seeking medical attention, and that the latter group runs a more rapidly downward course, including rapidly developing cachexia and asthenia. It is in this latter group that the evidence of adrenal hypofunction may be overlooked and in which further investigation may reveal an impressive incidence of Addison's disease. Although bronchogenic carcinoma presents the greatest incidence of adrenal involvement, one of our cases and a report of one in the literature<sup>3</sup> indicate that any malignancy which metastasizes to the adrenals may destroy the glands sufficiently to produce Addison's disease. An awareness of the condition is urged, particularly in those cases of bronchogenic carcinoma where the downward course is out of proportion to the primary lesion, i.e., where the course is that of untreated Addison's disease rather than that of metastatic carcinoma.

#### SUMMARY AND CONCLUSION

1. Addison's disease due to metastatic destruction of both adrenal glands probably occurs with much greater frequency than has previously been recognized. As evidence, three cases and a probable fourth are presented, collected during a two year period at one institution.

2. The failure to recognize the entity probably is attributable to the resemblance of the Addisonian picture to the cachectic state of advanced malignancy with widespread metastases.

3. More cases of Addison's disease due to metastatic adrenal destruction would be found if patients with primary cancer were investigated by endocrine, electrolyte and carbohydrate tolerance studies when the progression of the symptoms is out of proportion to the primary disease.

#### ACKNOWLEDGMENTS

We should like to express our appreciation to Dr. James R. Reuling, Dr. Alfred A. Angrist and Dr. Charles S. Byron, all of Queens General Hospital, for aid in the formulation of this paper.

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## REHABILITATION OF THE PATIENT WITH HEMIPLEGIA \*

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PATIENTS with hemiplegia constitute one of the largest groups of persons suffering from chronic neurologic defects. It has been estimated that there are more than 1,000,000 at any one time in the United States.<sup>1</sup>

As physicians, we have carefully treated the acute condition. If the patient survived, we have sent the patient home with little or no instruction as to his further care and rehabilitation. Some of these patients have been able to teach themselves to walk and have been able to resume a fairly normal life. At the Institute of Physical Medicine and Rehabilitation, we have found that many more can be benefited by an active treatment program under the direction of a physician.

Out of the first 200 cases of hemiplegia that have gone through the Department of Physical Medicine and Rehabilitation at the Bellevue Hospital and who were reviewed one year after discharge, it was found that 79.6 per cent were capable of self-care and 20.4 per cent were capable of some employment.<sup>2</sup>

*I. Selection of Hemiplegic Cases for an Active Rehabilitation Program:* Each individual patient must be carefully examined and evaluated from the point of view of whether a rehabilitation program is feasible. Cases are excluded that have (1) malignant hypertension, (2) encephalomalacia, (3) senility. Those patients who have a hemiplegia resulting from trauma are included in the rehabilitation program only when it is felt that they are clinically ready to start such a program. In addition, every patient selected must have the will power and motivation to start his treatment program. This is particularly true of the patient with hemiplegia, because it is not so important what we as physicians *do* for the patient, but, rather, what we teach the patient to do for himself. There must always be a careful evaluation of the mental as well as the physical resources of the patient.

There is always a question as to when is the proper time to start an active program for these patients. When the cause of hemiplegia is thrombosis or embolism, an active program can be started within two to three days. If cerebral hemorrhage has been the cause of hemiplegia, we used to wait two to three weeks before starting an active program, but lately we have shortened this period of time to five or seven days, according to the condition of the patient. It has become apparent that there has been no untoward effect from starting the rehabilitation program on an earlier date than heretofore.

*II. Initial Examinations:* Upon admission to the Department of Physical Medicine and Rehabilitation, every patient undergoes an initial physical

\* Presented at the Thirty-third Annual Session of the American College of Physicians, Cleveland, Ohio, April 25, 1952.

and mental survey. In addition, the three tests that are important for rehabilitation are included: the range of motion test, muscle test, and testing for the activities of daily living.

There are 102 ordinary activities of daily living for which every patient is tested: these include such things as speech, rolling from place to place in bed, feeding and toilet care, ability to sit on the edge of the bed, to stand and walk, to get from bed to wheelchair and back again, to climb stairs, etc. Every patient is asked to go through these activities; those he can accomplish are checked in black, those that he cannot are left blank, to be filled in later in red as the therapist teaches the patient this activity.

A simple procedure to test if the patient has sufficient muscular strength in the lower extremity to learn to walk again is to ask the patient while lying on his back to lift the partially paralyzed leg. If he is able to raise his leg one inch off the bed, he has enough muscle power to learn to walk again.

*III. Procedures to Prevent Deformity While the Patient Is in Bed during the Acute Phase, and Also to Be Followed during His Time in Bed before His Rehabilitation Program Has Been Started:*

1. A pillow should be kept in the axilla on the affected side at all times during the patient's stay in bed to prevent the adduction contracture of the arm to the side.

2. A foot board should be placed at the end of the bed or, preferably, a posterior leg splint should be applied to the paralyzed lower extremity to prevent foot drop on the affected side. The sheets should never be pulled tightly over the edge of the bed.

3. Sand bags should be placed laterally along the paralyzed leg to prevent outward rotation of the leg.

4. The joints of both affected extremities should be carried through a complete range of motion passively twice a day, once in the morning and once in the afternoon. The nurse or a member of the family can be taught to do this. Particular attention should be given to the shoulder joint, since this quickly tends to become ankylosed and painful.

5. Quadriceps muscle setting should be carried out actively by the patient, to maintain and increase the strength of this muscle group. This should be done for 15 minutes twice daily.

*IV. Treatment Program:* Within the time limits as set forth above, the first activity for the patient should be to learn to sit upright in bed. At first, this will probably have to be with assistance. A small rope made of braided bandage is tied to the end posts of the bed and brought up two thirds of the patient's length in bed. This is arranged so that he may grasp it easily with his good hand. He should be taught to place the paralyzed hand on the rope and hold it in position with the good hand and use both arms to pull himself up to a sitting position. It is important that the patient start sitting up in bed and, later, on the edge of the bed with the legs hanging over, to preserve his sense of balance. These patients lose their sense of balance very quickly if they are kept lying quietly in bed for any length of time.



Standing by the side of the bed,—this can be done with parallel bars. The patient grasps the bar with the good hand and the nurse or attendant places the paralyzed hand on the parallel bar. If parallel bars are not available, two ordinary kitchen chairs may be put beside the bed with their backs to each other, two feet apart. The patient is taught to place the paralyzed hand on the top of the chair. The hand can be bandaged to the top rung of the chair if he is unable to grasp it. After a few days of standing and shifting his weight from one leg to the other, and when the sense of balance has returned, is the time for him to start learning to walk again. This must be done with a reciprocal motion. As the right hand is extended along the parallel bar, the left lower extremity is brought forward. As the left hand is advanced along the parallel bar, the right lower extremity is brought forward, in order that the patient will walk with a normal reciprocal pattern. If chairs are used, an attendant stands on the paralyzed side of the patient and advances one chair while the patient moves the other chair with the good arm and hand. The pattern should be the same—right foot, left hand advanced; left foot, right hand advanced.

A short leg brace should be prescribed for every hemiplegic patient who has a foot drop or toe drag. To allow a patient to try to walk with a toe drag or an inversion of the foot is a hazard. These patients are unstable on their feet and, if they stub a toe or twist an ankle, they are likely to fall, with resultant fracture. A simple light double-bar short leg brace with a 90 degree stop gives them security, prevents toe drop and toe drag, and facilitates progress in walking. After learning to walk on level surfaces, they must be taught to climb stairs and curbs. Some patients may need long leg braces to stabilize the knee.

The aphasic patient should be given treatment early by a speech therapist. This is a long continued treatment program.

Many patients with hemiplegia have a very painful shoulder on the side of the paralysis. These patients usually have very restricted range of motion in this joint. In such cases we have found the following procedure helpful. A pulley is attached to a wall at a level above the patient's head, and a line passed through the pulley. The patient is seated in a chair below the pulley. One end of the line is attached to the paralyzed hand and arm (carefully bandaged so that there is no abrasion of the skin). To the other end of the line a small handle is attached, and this the patient grasps with his good hand. He can now pull down with the good arm and hand and so bring the paralyzed arm up in extension. The pain will not allow him to go too far, but he is encouraged to increase the range of motion in the shoulder joint every day. This exercise is done for 15 minutes twice daily. We have found that when normal range of motion is actively or passively accomplished, the pain disappears from the joint.

*Personal Care Activities:* These patients can be taught to take care of their personal needs, personal cleanliness, to dress themselves, even to button



their buttons and tie their own shoestrings with one hand. This is usually accomplished under the direction of a physical therapist.

#### SUMMARY

Many patients with hemiplegia can be taught to walk again, to take care of their personal needs and even to return to work. The problems of the hemiplegic patient should be approached by a total treatment program, and this must be directed by his physician.

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## THROMBOTIC OBLITERATION OF THE ABDOMINAL AORTA: A REPORT OF SIX CASES \*

By WILLIAM E. BARNETT, M.D., F.A.C.P., *Dallas, Texas*, WARREN W. MOORMAN, M.D., *Fort Worth, Texas* and BEN A. MERRICK, M.D., *Dallas, Texas*

THROMBOTIC obliteration of the abdominal aorta was first described by Graham,<sup>1</sup> who in 1814 reported a museum preparation of an aorta "plugged up with a laminated coagulum just above the bifurcation of the iliac arteries into which this substance extends." The history of this case was not available. In 1899 Welch<sup>2</sup> reported 59 cases of embolism and thrombosis of the aorta, of which 14 were said to have been due to thrombosis. In 1921 Hesse<sup>3</sup> summarized 73 cases of obliteration of the aortic bifurcation, of which thrombosis was responsible for 11. Subsequently, isolated case reports<sup>4-18</sup> and small series or reviews<sup>19-25</sup> have appeared. Many of these articles make no clear differentiation between thrombosis and embolism of the terminal aorta. Only 76 of the cases which were adequately confirmed by autopsy, surgical operation or arteriogram are thought to represent thrombosis in accord with the following criteria.

### THE DIFFERENTIATION OF THROMBOSIS FROM EMBOLISM

Usually the onset of thrombosis of the terminal aorta is gradual, accompanied by a subtle development of symptoms. This is quite unlike the saddle or rider embolus, whose victim is suddenly stricken with severe pain and cyanosis of the lower extremities. An exception, according to Rothstein,<sup>17</sup> is the thrombus which occludes the aorta without producing symptoms until the narrow channel suddenly becomes obliterated. In this way, thrombosis may manifest itself abruptly. Another differentiating factor is the duration of symptoms. Commonly, thrombosis presents symptoms of months' or years' duration. The patient with embolism of the aorta and iliac vessels usually suffers only hours or days. Rarely, without surgical intervention, does a case of embolic obliteration of the aortic bifurcation recover from the acute episode and develop chronic arterial insufficiency in the lower limbs. Antecedent embolic phenomena favor the diagnosis of embolism. Most of the cases of embolism involving the aorta have infarctions in upper extremities, kidney, spleen or other viscera. In nearly all embolic occlusions of the abdominal aorta there is an antecedent history of mitral stenosis, auricular fibrillation or myocardial infarction to account for a source of emboli. In this connection, one must remember the syndrome

\* Received for publication October 19, 1951.

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of essential thrombophilia described by Nygaard and Brown,<sup>27</sup> consisting of multiple arterial occlusions which might easily be mistaken for embolism. In thrombosis there is, in the great majority of cases, a local pathologic change in the aorta at the site of the thrombus.

#### INCIDENCE

In 4,394 autopsies performed at four hospitals in this area, covering 10, 10, seven and four years, respectively, there was a total of 10 cases listed as thrombosis of the aorta. Five of these showed complete thrombosis, all occurring in the abdominal aorta. The remaining five cases showed incomplete obstruction of the aorta and were described as mural thrombi, or laminated thrombi of a saccular aneurysm, and in themselves had no recognizable clinical symptoms. Three of the herein reported cases of complete obstruction were seen within a year. Gross and Phillips<sup>19</sup> reported four cases out of approximately 5,350 autopsies. Straus et al.<sup>28</sup> reviewed cases representing approximately 15,000 autopsies, of which 21 were considered to represent thrombosis of the abdominal aorta. Of these 21 cases, the nine reported by Siegel and Garvin<sup>30</sup> probably were embolism rather than thrombosis. The condition has been described in all age groups, but occurs most commonly in the fourth to sixth decades of life. More than 90 per cent of the reported cases have been males.

#### CLINICAL PICTURE

A clinical syndrome of thrombotic obliteration of the aortic bifurcation was first described by Leriche<sup>28, 29</sup> in 1940. The essential features of his description are as follows:

A prolonged insidious period of development was the characteristic feature of this syndrome. This has been our experience in the six cases herein reported. Unstable penile erection was reported in all of the recent French and Spanish cases. This symptom was present in only one of our patients, and has been described by no other American authors except Elkin and Cooper.<sup>24</sup> Five of their 10 cases complained of some degree of impotence. The impaired circulation of both lower limbs was characterized as weariness, in contradistinction to the pain of intermittent claudication. Although this distinction could be made in cases 1 and 3 of this report, the other four cases and the vast majority of the other reported cases had intermittent claudication as well as easy fatigability. Indeed, the four cases Leriche reported had painful cramps in the legs on walking or running. Atrophy of the lower extremities with absence of frank trophic changes was present. In the late stages of the disease, Leriche also observed cyanosis of the legs and feet, desquamation of the skin and ulcers at points of pressure. In this stage there may be extreme pain. Gangrene may develop. Leriche attributed the terminal stages to extension of arterial thrombosis and associated venous thrombosis. Pallor of the legs and feet, even when the

patient was standing, was described by Leriche. Although extreme pallor on elevation has been observed in this series, pallor on standing has not been reported by American writers. Aortic pulsations were not palpable in the abdomen except high above the umbilicus, and pulsations were absent in the thighs, legs and feet. Although this was the usual finding, an occasional patient (cases 1 and 2) may have unilateral or bilateral femoral pulsations produced by very large anastomoses to the femoral artery. Oscillometric findings revealed no oscillations in the leg or thigh. This was the usual experience, but collaterals may be adequate to permit blood pressure recordings below the occluded aorta (case 1). Arterial tension was moderately elevated in the upper extremities. This was a very common finding but by no means universal. Frequently the blood pressure was quite high. This is not surprising in view of the acknowledged frequency of atherosclerosis in hypertensive individuals.

#### ETIOLOGY

Atherosclerosis of the abdominal aorta was far the commonest underlying condition of thrombosis, the thrombus being frequently attached to ulcerated atherosclerotic plaques. Other predisposing factors described were arteriosclerotic or syphilitic aneurysms, dissecting aneurysm of the aorta, trauma to the lower abdomen, uterine neoplasms and neoplasms of the lumbar vertebrae.<sup>3,14</sup> Cases reported in infants have been secondary to umbilical sepsis. Congenital narrowing of the terminal aorta has been blamed by some for thrombus formation, but Leriche<sup>28</sup> maintained that the narrowing frequently observed distal to the occlusion was secondary to the thrombosis. He has pointed out that thrombosis may begin in the iliac arteries and propagate proximally to obliterate the abdominal aorta. Vascularization of the intima and media at the site of an atheroma, with subsequent hemorrhage and rupture into the lumen, has long been recognized as a cause of thrombus formation in small and medium arteriosclerotic arteries. Recently Wartman<sup>25</sup> described a case in which this was demonstrated as the responsible mechanism for causing a thrombosis of the abdominal aorta with complete obstruction.

#### DIAGNOSIS

Chronic thrombotic obliteration of the abdominal aorta must be differentiated from other conditions in which the patient complains of easy fatigability of the legs or intermittent claudication, with diminished or absent pulsations in the lower extremities. Coarctation of the aorta may be ruled out by the absence of rib-notching, the presence of a normal aortic arch in the chest x-ray, and x-ray demonstration of calcification of the abdominal aorta. Atherosclerosis with calcification of the aorta distal to coarctation is said to be relatively uncommon.<sup>31</sup> Difficulty in differentiation may arise in the rare case of coarctation occurring distal to the usual site, especially the subdiaphragmatic type as reported by Bahnson et al.<sup>28</sup> In

such instances, clinical differentiation may not be possible and resort to an arteriogram may be necessary.

Arteriosclerosis obliterans in the legs occurs in the more aged; trophic changes and gangrene appear relatively early. Pulsations in the entire abdominal aorta are palpable. Sclerotic changes in the dorsalis pedis artery may be detectable. Thromboangiitis obliterans may be differentiated to some extent by a history of phlebitis, commonly present in Buerger's disease. Pain is a much earlier symptom in this condition. Although common in Buerger's disease, rubor with dependency is rare in aortic thrombotic obliteration.

Aneurysm of the abdominal aorta will usually manifest itself as a pulsatile abdominal tumor. Erosion of vertebrae by the aneurysm can frequently be demonstrated by x-ray examination. Déjérine's syndrome is suggested by loss of sexual power and weakness of the lower extremities. This condition is attributed to progressive occlusion of the arteries supplying the lower spinal cord. This syndrome has received experimental confirmation in the work of Reichert et al.,<sup>22</sup> who produced claudication in the hind legs of dogs by ligation of the lumbar segmental arteries. These authors reported four cases in which arteriosclerosis of these vessels was thought to account for weakness of the lower limbs, loss of libido and premature ejaculation. The presumptive diagnosis of thrombotic obliteration of the abdominal aorta is confirmed by the arteriogram<sup>23</sup> which was originally described by Dos Santos.<sup>24</sup> This procedure has now been performed in enough cases that it can be carried out with very little risk.

#### PROGNOSIS

The prognosis in thrombotic obliteration of the terminal aorta is guarded. Gangrene of feet and legs frequently eventuates in amputations. Death usually occurs from progression of the underlying generalized arteriosclerotic vascular disease or by propagation of the thrombus. Recent surgical approaches seem to have a definite beneficial effect.

#### TREATMENT

The treatment outlined by Leriche was directed toward improvement of the peripheral circulation through reduction of the vasoconstrictor nerve supply of the collateral and distal blood vessels. This was accomplished by upper lumbar ganglionectomy. Surgical removal of the thrombotic zone has been recommended, this resection being designed to abolish possible constrictor impulses originating in the diseased aortic wall. However, due to the sclerotic nature of the aortic wall, this procedure is rarely possible with present day methods. Sympathectomy as a treatment was conceived incident to the experimental work of Stricker and Orban.<sup>25</sup> Animals subjected to aortic resection suffered paralysis of the hind legs, gangrene and death. Animals sympathectomized before resection survived and reestab-

lished a satisfactory circulation. In 1948 Leriche reported 19 surgically-treated cases, Servell one, Moulonget one, Martorell three, and Elkin and Cooper five.

#### CASE REPORTS

*Case 1.* A 47 year old policeman was seen by one of us in September, 1948, with the following complaints: (1) severe bitemporal and frontal headaches with nausea, vomiting and double vision; (2) extreme tiredness and weakness in legs on walking a short distance and, more recently, shortness of breath on exertion; (3) loss of sexual powers, and (4) nocturia.

The patient dated the onset of his symptoms from 1941, when he became employed as a war worker. Previous to 1941 patient stated that, as a farmer, he could do a day's work behind a walking plow. He noted that walking from the parking lot to his site of work caused an extreme sense of tiredness in both legs but no frank pain. This condition of his lower extremities continued without remission but with no increase in the intensity of symptoms for seven years. In May, 1945, the patient became a policeman, riding in a patrol car, in which situation he carried on well until May, 1948, when a change in assignment necessitated some walking. In this situation he found it necessary to do as little walking as possible, because of the leg symptoms. Also, he related a tendency to keep his thumbs in his Sam Browne belt, pulling his belt away from his abdomen to relieve a pressure there. For a short period of time he complained of tenderness about the umbilicus. The patient stated that for the last three years his feet had always been cold. Nocturia (five times) had been present for two or three years. There was a loss of penile erection for a period of two years, preceded by a gradual decline in sexual performance over a period of 15 years.

Dating from early 1946, headaches had increased in frequency and intensity, along with blurred vision. An ophthalmologist discovered arterial hypertension in January, 1948. Gradually episodes of nausea and vomiting appeared with the head pain. In September, 1948, patient experienced diplopia which lasted for three days. Later examination revealed a hemorrhage into the right retina.

Past history was noncontributory except for records of City civil service physical examinations in May, 1945, and November, 1946, which did not reveal hypertension.

Physical examination revealed a white male, 71 inches tall, weighing 148 pounds. There was visible tortuosity of the temporal arteries. Retinal examination revealed bilateral papilledema of about 1 diopter. There were considerable arterial spasm, A-V nicking and a small hemorrhage in the right retina. Extrinsic ocular muscles were normal. The chest and heart were within normal limits. Blood pressure of the upper extremities was 230/130 mm. of Hg. and of the lower extremities, 120/80 mm. of Hg; however, at later examinations the blood pressure of the lower extremities could not be obtained. The abdomen was scaphoid, and a pulsation could be felt at a point three fingerbreadths below the ensiform process. A systolic bruit was heard at this point. No pulsations lower in the abdomen could be felt. There were no pulsations in the left femoral artery, and very faint pulsation in the right femoral artery. Pulsations of the dorsalis pedis and the posterior tibial arteries usually were not felt; however, on several occasions weak pulsations were felt. The patient had a small waist and narrow hips, and a lack of muscular development of legs as compared with arms and shoulders. Deep reflexes and sensory tests were normal. No trophic skin changes were present. With patient supine, elevation of limbs soon caused the feet to have a translucent whiteness. Oscillometric indices of both lower extremities ranged from 1.5 to 0. X-ray examination of the chest showed increase in long and transverse diameters of the heart. Notching of ribs was absent. The electrocardiogram was normal except for left axis shift. Urine examination revealed specific

gravity, 1.008 and 1.016; albumin, trace; and numerous coarsely granular casts. Serologic tests for syphilis were negative.

A tentative diagnosis of coarctation of the aorta was held at this time, and the patient was submitted to an angiogram at Parkland Hospital as an outpatient. The findings were negative for a coarctation or other abnormalities of the thoracic aorta. The presence of a pulsation in the midline of the upper abdomen, the absence of lower abdominal or femoral pulsations, absence of abdominal mass or pain, and negative



FIG. 1. Arteriogram of case 1, showing obstruction of aorta below renal arteries and collateral pathways of the circulation.





FIG. 2. Postmortem x-ray showing injection of aorta, obstruction and collateral channels of circulation to the pelvic viscera and lower extremities.

findings in the angiogram suggested the diagnosis of an obliterative lesion of the lower abdominal aorta. Accordingly, on December 21, 1948, an arteriogram was performed by Dr. Keller Doss, of Fort Worth, Texas, employing a technic described elsewhere<sup>23</sup> (figure 1). The arteriogram revealed an obstruction just below the renal arteries. The right renal artery was visualized but the left seemed to be involved in the process. The upper lumbar arteries and subcostals were visualized, and provided collateral pathways to the lower extremities.

The patient steadily deteriorated. The attacks of nausea, vomiting and visual disturbance came more often. At times the patient was in a stuporous state. He was admitted to St. Paul's Hospital January 3, 1949, having repeatedly refused hospitalization previously. Physical findings were essentially the same on admission as enumerated above, except for dehydration.

Laboratory studies revealed a maximal urine concentration of 1.016. Blood chemistry was normal except for a  $\text{CO}_2$  combining power of 40 vol. per cent. The spinal fluid had a protein of 75 mg. per cent. Wassermann, Kline and Eagle tests were negative. Prothrombin time was 16 seconds.

Management consisted of the slow infusion of Hartman's solution in 1,000 c.c. glucose and distilled water. Within 24 hours the patient became rational. On January 13, 1949, a lumbar sympathetic block was done with procaine. There was no increase in oscillometric indices or skin temperature of the lower extremities. On January 18, 1949, the patient became nonresponsive and had a small convulsive movement over the entire body. The Babinski sign became bilaterally positive. The patient died January 20, 1949.

*Autopsy Findings:* The heart weighed 425 gm., and the left ventricle was markedly hypertrophied. The coronary arteries were patent throughout, and the valves were normal. Previous to removal of the aorta, 250 c.c. of saturated solution of sodium iodide were injected into the thoracic aorta and x-ray films were made

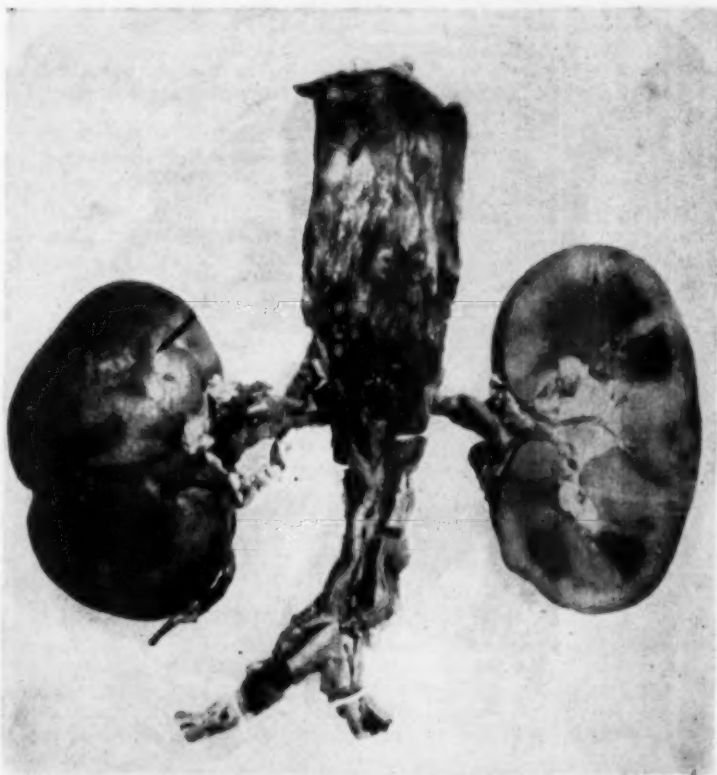


FIG. 3. Gross specimen of case 1.

(figure 2). These studies revealed an obstruction of the abdominal aorta at the level of the second lumbar interspace. The superior mesenteric artery, branches of the celiac artery, and the right renal artery were visualized, but the two arteries of the left kidney could not be seen. The subcostal arteries were greatly dilated, and the major collateral for blood to pass to the lower extremities was provided by these arteries anastomosing with the deep circumflex iliac artery. The collateral circulation to the abdominal viscera, pelvic viscera and lower extremities was found to consist of an anastomosis of the subcostal artery with the lumbar branch of the iliolumbar artery; also, the iliac branch of the iliolumbar anastomosed with the deep circumflex iliac artery. In this fashion the superior and inferior gluteal, lateral sacral and internal pudendal arteries received blood from above the thrombotic obstruction. The thoracic aorta was normal; however, the abdominal aorta showed moderate atherosclerosis without ulceration. From a point 1 cm. below the renal arteries a large thrombus was seen to extend distally, completely filling the aorta and causing it to



FIG. 4. Photomicrograph of thrombosed abdominal aorta, case 1.

bulge. This process, showing various degrees of organization to complete fibrosis, extended down the common and external iliac arteries to a point near the inguinal ligaments. The diameter of the aorta at the proximal portion of the thrombus measured 2.5 cm.; the distal portion was smaller (figure 3). Dissection of the upper abdominal aorta revealed no residuals at the site of the aortic puncture for arteriogram. The renal vessels apparently were not involved. The distal portion of the abdominal aorta and the common and external iliacs were completely obliterated by an old brownish white thrombus.

The right kidney weighed 170 gm. and the left 232 gm. The left kidney had a double renal artery. The capsules stripped with ease and, on section, no gross architectural changes were observed.

The brain appeared soft and edematous. The basilar arteries were diffusely thickened. On section there were small areas of softening in the white matter.

Microscopic examination of segments of the thrombosed abdominal aorta showed sclerotic thickening of the intima to which a thrombus in various stages of organization was attached (figure 4). There were a few attempts at canalization. The thrombus at some points showed rather advanced organization and at other points was amorphous, and cholesterol crystals were present. There was no unusual reaction in the vasa vasorum. The brain showed numerous small areas of softening. The kidney showed passive congestion, marked degeneration of tubules, and arteriosclerosis with atrophy of some of the glomeruli.

*Comment:* The cause of death in case 1 was encephalomalacia, hypertensive heart disease with chronic failure, and bronchopneumonia. Except for the terminal pneumonia, the other causes were a manifestation of a diffuse arterial disease. The history of lower extremity symptoms without dramatic onset, associated with the autopsy findings of an organized thrombus in the abdominal aorta and well developed collateral circulation to the lower extremities, indicated a slow, progressive thrombosis of the abdominal aorta. There were no episodes in the history and no gross or microscopic findings in the aorta that could account for the inception of the process, except for atherosclerosis. There was present a definite train of symptoms and physical signs that reasonably conformed to the syndrome first reported by Leriche in 1940. The appearance of hypertension after 1946 makes its occurrence probably coincidental. No efforts at therapy, such as lumbar sympathectomy or resection of the thrombosed aorta, were carried out, due to refusal of the patient to be hospitalized until a terminal state was reached.

*Case 2.* A 39 year old white man was admitted to the McKinney Veterans Hospital August 17, 1948, complaining of increasingly severe episodes of exertional and paroxysmal nocturnal dyspnea since February, 1948. Several days before admission he had first noted swelling of his feet and ankles. In February his condition was diagnosed in another hospital as hypertensive heart disease secondary to coarctation of the aorta. Since childhood his left lower extremity had been cold in the winter. In 1942 he developed intermittent claudication of the left calf. This persisted and became more severe. He had lost 35 pounds in weight during the past six months. Nocturia (two to three times) had been present for about three years. In 1932 he had had gonorrhea, and in 1940 he developed urinary retention from a urethral stricture which was dilated.

Physically he was an orthopedic male who appeared to have been chronically ill. There were grade I changes in the retinal arteries. The chest was emphysematous,

and there was a small amount of fluid in the right lung base. A to-and-fro vascular murmur could be heard at the tip of the right scapula. The heart was enlarged 2 cm. beyond the midclavicular line in the left fifth intercostal space. The rhythm was regular. There was a faint diastolic blowing murmur heard in the third intercostal space at the left sternal margin. Blood pressure, left arm, 180/112 mm. of Hg; right arm, 184/116 mm. of Hg; left leg, not obtainable; right leg, 154/120 mm. of Hg. The right femoral artery pulsations were palpable at the inguinal ligament only. No other vessels could be felt to pulsate in the lower extremities. The feet and legs were cool. The nails were cyanotic. There was pitting edema of the feet and ankles.

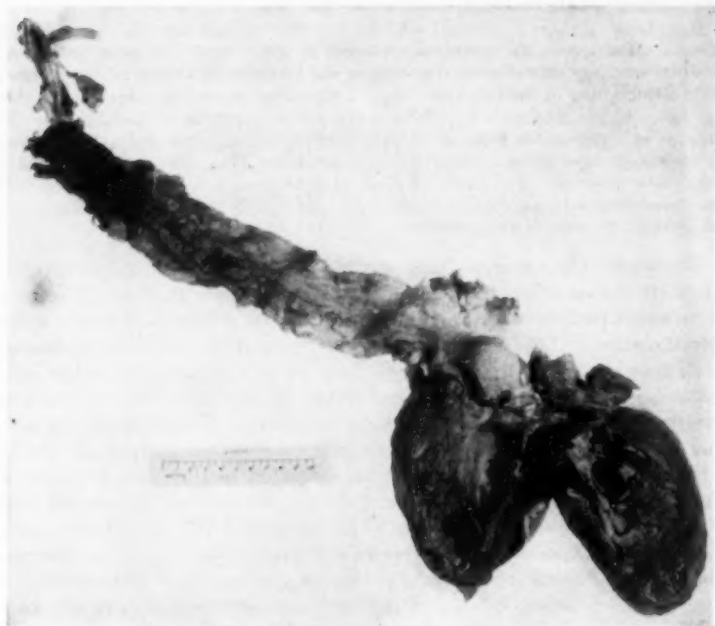


FIG. 5. Gross specimen of case 2.

There were no trophic changes. The feet were very pale when elevated, but there was no rubrocyanosis with dependency. There were dilated, tortuous, vigorously pulsating subcutaneous arteries over the sides of the chest and abdominal walls. These seemed to communicate between intercostal and femoral arteries bilaterally.

Laboratory studies revealed persistent albuminuria, and granular casts in a urine of rather fixed specific gravity. There were no red cells in the urine. Total and differential leukocyte counts were within normal limits. Serologic tests for syphilis were negative. Blood urea nitrogen was 34 mg. per cent. X-ray examination of the chest demonstrated a cardiothoracic ratio of 17 cm./29 cm., with enlargement of the left ventricular type. There was no rib notching. The entire thoracic aorta appeared normal. The abdominal aorta was visualized with large amounts of calcium in its walls. Electrocardiogram was abnormal because of QRS wave changes which

represented impaired intraventricular conduction. The response to treatment was prompt, so that the patient was released from the hospital to await further studies. In 17 days he returned with severe congestive failure and a greatly dilated heart. There was electrocardiographic evidence of a recent anterior apical myocardial infarction. Leukocytes numbered 31,200, with a left shift of the Schilling index. Blood cultures were sterile. He continued to fail rapidly and died October 19, 1948.

The significant necropsy findings were limited to the cardiovascular system and kidneys (figure 5). The heart weighed 700 gm. There were mural thrombi in each auricular appendage. The left ventricular wall was thickened, and at the apex there was found softening of the myocardium beneath a mural thrombus and an area of fibrinous pericarditis. This portion of myocardium, involving the lower one-third of the interventricular septum and the left ventricle at the apex, was dark gray.

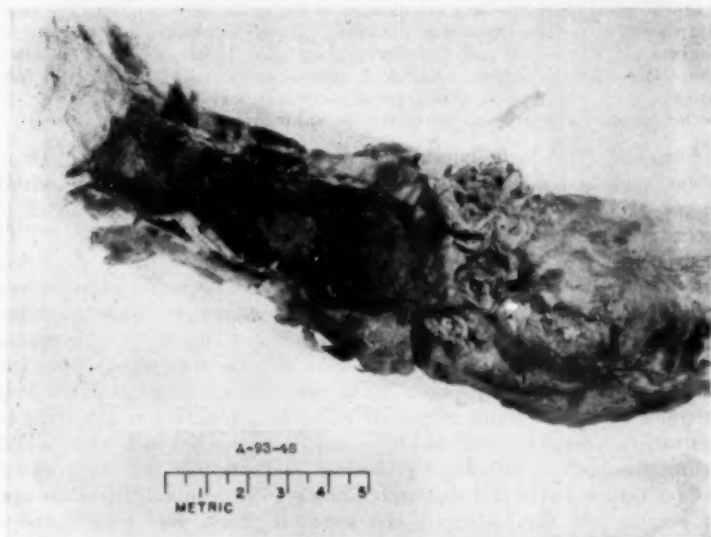


FIG. 6. Gross specimen of case 2, showing obliterative thrombus in situ.

There was a thrombotic occlusion of the anterior descending branch of the left coronary artery 3 cm. from its origin. The right coronary artery was completely occluded 1.5 cm. from its origin by calcified atherosclerotic plaques. The entire thoracic aorta was involved with advanced atherosclerosis. The abdominal aorta below the renal vessels was very firm, and the iliacs were very small, measuring approximately 3 mm. in diameter. Upon opening the abdominal aorta, a firm thrombus of grayish brown appearance was found originating in the common iliac arteries slightly distal to the bifurcation of the aorta and extending upwards, terminating in an unattached tail-like process 1 cm. above the renal arteries (figure 6). Both renal arteries had thrombi extending into them about 1.5 cm. The left renal artery was more occluded than the right. The aortic thrombus below this level could not be dislodged without removing the intima as well. The superior mesenteric artery was completely occluded. The inferior mesenteric artery could not be identified. There was far

advanced calcification of the aorta in this area, but the thrombus itself did not appear to be calcified. The inferior epigastric and deep circumflex iliac arteries were greatly increased in size, particularly on the right.

The combined weight of the kidneys was 200 gm. Microscopic section of the left kidney revealed a histologic picture entirely different from that on the right. In the left kidney hyperplastic or proliferative arterioles and smaller arteries were found with ease. In some instances there was fibrinoid degeneration in the wall of these altered vessels. The changes were those of malignant nephrosclerosis. Sections of the right kidney differed from those of the left in that arteriolar and small artery change was lacking. Very careful search revealed only a questionable hyperplastic arteriole, but certainly not of the proportion seen in the opposite kidney. In sections of the right kidney, a large, antemortem, slightly organized thrombus was seen in a large vessel, apparently the renal artery. Section of the aorta through the organizing thrombus revealed extensive calcification of the media extending into the intima and apparently into the organizing thrombus. It was impossible to determine the zone between vessel wall and thrombus. Many cleft spaces indicated cholesterol within atherosclerotic plaques. Advanced atherosclerotic changes were also found in microscopic study of celiac axis, superior mesenteric and both renal arteries. The superior mesenteric artery was completely occluded by an organizing thrombus.

*Comment:* This represents a case of slowly progressive thrombotic occlusion of the abdominal aorta. This man's history of coldness and claudication of the left leg for many years indicated the long duration of the process. The absence of an acute episode makes embolism unlikely. The extensive collateral circulation, with large superficial arteries, mimicking those found in coarctation of the aorta and other collaterals which allowed the bowel to survive after the occlusion of the superior mesenteric artery, is possible only with a very chronic obliteration. The resulting hypoplasia of the iliac vessels has been shown by Leriche to be a result of obliteration rather than congenital hypoplasia. The asymmetrical findings in the lower extremities were the result of greater collateral circulation to the right leg. This patient's death is attributed to extensive myocardial infarction. There is clinical as well as pathologic evidence to indicate that this occurred only 18 days before death, and that embolization from a mural thrombus could not account for the findings. His terminal illness was complicated by uremia due to arteriolar nephrosclerosis.

*Case 3.* A 65 year old white male entered Baylor University Hospital on August 25, 1949, complaining of marked shortness of breath. This began three weeks before admission as an attack of paroxysmal nocturnal dyspnea. Aminophylline gave some relief from the dyspnea. He stated he had always had low blood pressure before his present illness.

Six years previously, while inspecting oil wells, the patient had noted onset of a numbness and weakness in both legs. This weakness of his lower extremities continued, and a few months after the onset he noted enlarged blood vessels on his abdominal wall. The weakness had reached the point where he could walk only about a block before developing an overwhelming feeling of weakness and numbness in his lower extremities, but there was no true pain in the calves. A 20 to 30 minute rest was required before he could walk further. Ligation (elsewhere) of the left saphenous vein four and one-half months before admission had not helped him.

Physical examination revealed a thin, dyspneic male. The blood pressure was



180/94 mm. of Hg. in the right arm, 182/98 mm. of Hg in the left arm, and was unobtainable in either lower extremity. Fundi revealed moderate narrowing and tortuosity of the arteries, but no hemorrhages or exudates were seen. The superficial veins of the neck were moderately distended. The lungs revealed basal râles and roughened breath sounds. The heart was not enlarged. A grade II systolic murmur was heard at the aortic and pulmonic areas, being transmitted into the neck. The rhythm was regular. There was tenderness to palpation over the liver area. Inspection of the anterior abdominal and chest walls revealed the presence of tortuous arteries coursing downward from the end of each fifth costal interspace to the umbilicus (figure 7). Descending from a point in the midaxillary line at the level of



FIG. 7. Clinical photograph of case 3, showing collateral circulation in abdominal wall.

the eleventh rib to the saphenous opening were two other tortuous arteries. Each of these measured 3 mm. in diameter and could be seen and felt to pulsate. There was a deep pulsation in the epigastrium, but none at or below the umbilicus. Pulsations could not be felt in the iliac arteries or in any artery of either lower extremity. The lower limbs felt cooler than the remainder of the body. There was no peripheral edema.

On admission the circulation time (Decholin) from arm to tongue was 25 seconds, the venous pressure 14.5 cm. of water, and the vital capacity 52 per cent of normal. An electrocardiogram revealed evidence of recent myocardial infarction. Chest x-ray revealed bilateral pulmonary emphysema and fibrosis of moderate severity, a calcific aortic plaque and a cardiac silhouette which was not enlarged or suggestive of a valvular lesion. Notching of the ribs was not present. A film of the abdomen revealed definite calcification in the wall of the abdominal aorta.

Laboratory studies revealed 14.6 gm. hemoglobin; 9,800 leukocyte count, with a normal differential count; a sedimentation rate of 10 mm. in 60 minutes, and negative Wassermann test. Three urinalyses were negative for albumin, sugar, casts or pyuria, the highest specific gravity being 1.019.

An arteriogram was performed by Dr. Dale J. Austin by injection of Diodrast into the proximal end of the abdominal aorta. The celiac, renal, superior mesenteric and lower intercostal arteries were demonstrated. A complete obstruction of the aorta was seen just distal to the superior mesenteric artery at the first lumbar interspace (figure 8).

There was marked improvement in the patient's dyspnea on digitalis administration and bed-rest. The possibility of a sympathectomy was considered but, because of the patient's poor general physical condition and his reluctance to undergo such a procedure, it was never done. The patient has not been heard from since his discharge from the hospital on September 6, 1949.

**Case 4.** A 40 year old watchmaker was first admitted to Parkland Hospital on October 30, 1945, with symptoms of severe headache and dyspnea on exertion for six weeks, and a rather sudden onset of orthopnea and gripping substernal pain of six hours' duration. Past history revealed that in 1932 he had fallen under a train in Fort Worth, Texas, with resulting left leg amputation at the mid-thigh. Several revisions of the stump were necessary to effect healing. In 1934 there was an amputation of the right leg below the knee for what was described as mummification. He had been known to have hypertension since 1941, when he consulted a physician concerning severe occipitofrontal headaches. Systolic blood pressure was 200 mm. at that time. In 1942 he was told that his heart was enlarged, and during that year he had several transient episodes of weakness in the left arm, which completely cleared.

On admission examination he was acutely ill, orthopneic, coughing and complaining of substernal chest pain. Fundi revealed grade II retinal artery changes and optic atrophy. There were moist râles throughout the lungs. The point of maximal impulse of the heart was in the anterior axillary line; the rate was 110 and regular, and there was a grade I systolic murmur at the aortic area. There was a high left thigh amputation, and the right leg was surgically absent below the knee. No comment was made concerning pulsations of the aortic or femoral vessels. Electrocardiogram revealed left ventricular strain pattern. He responded promptly to opiates and digitalization. It was thought that the chest pain was due to myocardial anoxemia and that there had been no myocardial infarction. He was discharged symptom-free 11 days after admission, receiving maintenance doses of digitalis. He was subsequently re-admitted in November, 1945, and August, 1946, because of a fracture of the neck of the left femur which he received from a fall. The first hospitalization was for insertion of a Smith-Petersen's nail, and the second for removal of the nail. No comment was made concerning pulsations in abdominal or femoral artery. Blood pressure in August, 1946, was 220/180 mm. of Hg. He was again



FIG. 8. Arteriogram of case 3, showing obstruction of the abdominal aorta.

admitted in October, 1946, for progressive severity of a dull occipital headache, severe cough, orthopnea, temporary episodes of blindness in the right eye, gripping substernal pain, malaise and weight loss.

Physical findings were essentially unchanged from his previous admissions. His response to treatment was poor, and he was discharged to a convalescent home. On November 11, 1947, he was readmitted, markedly dyspneic, pale and sweating, with many râles. Blood pressure was 258/153 mm. of Hg; blood urea nitrogen, 150 mg. per cent; temperature, 101.2° F. He became rapidly irrational and finally comatose;

his urine output decreased, and the blood urea rose. He developed Cheyne-Stokes respiration. His temperature rose terminally to 105° F., and he died quietly on the fifth hospital day.

*Autopsy Findings:* The body was that of a 42 year old white male. The heart appeared to be grossly enlarged and weighed 586 gm. The ostia of the coronary arteries were patent. Numerous yellow, raised atheromatous plaques were present in the thoracic aorta. There was slight passive hyperemia of the lungs and chronic passive hyperemia of the liver. The kidney capsules stripped with ease, revealing a very granular stippled surface. The abdominal aorta at a point approximately 3 cm. above the bifurcation contained a thrombus which completely occluded the lumen of the aorta. This thrombus extended upward for a distance of approximately 8 cm. It was firmly adherent to one side of the wall of the aorta, grayish white in color and moderately firm in consistency.

Microscopic examination of the aorta revealed the intima to be much thickened, and in most areas the intima had been replaced by a pale hyaline material which was devoid of cells. In this hyaline material were many cleftlike spaces representing cholesterol deposition. In the media there were focal infiltrations of lymphocytes, most prominent about the small arterioles in the wall of the aorta. The media was atrophic and there was a considerable amount of hyaline material deposited here. In many areas the elastic fibers were broken up. The small arterioles in the wall of the aorta showed considerable thickening and an endarteritis obliterans. Attached to the intima and apparently originating from atheromata was a large thrombus composed of fibrin platelets and a few red blood cells.

The final diagnosis was arteriolar nephrosclerosis, myocardial hypertrophy, coronary atherosclerosis, purulent bronchitis and arteriosclerosis of the abdominal aorta, with a large thrombus occluding the abdominal aorta.

*Comment:* It is significant that after the left leg injury and amputation there was a series of five operations to effect a healed stump. In 1934, at Corsicana, Texas, the left leg was amputated just below the knee for what was described as mummification. It is reasonable to believe that the thrombotic process was of long standing and of gradual onset, because there was no history suggestive of a recent vascular accident; the difficulty in the management of the stump in 1932 and loss of another leg in 1934 may well have been due to an aortic thrombosis 13 years before death.

*Case 5.* A 66 year old white male was admitted to Parkland Hospital on August 3, 1942, complaining of severe generalized abdominal pain beginning about 24 hours prior to admission. With the onset of the pain he had had a normal bowel movement and vomited; he had sweated profusely, felt very cold and been more dyspneic than usual. He had had four severe attacks of abdominal pain, each followed by a bowel movement and vomiting. Since the onset of the pain he had had increasing shortness of breath, although he had been short of breath continuously for the past two or three months. In a previous hospitalization he gave a history of dyspnea and orthopnea, with occasional precordial pain since 1937. In January, 1940, the patient noted gradual onset of pain in left foot and leg. On walking there was an exacerbation of pain in the left toes and right hip. Incident to trauma, an ulcer developed on the left great toe, followed eventually by gangrene. There was a left mid thigh amputation June 11, 1940. There was a sudden onset of pain in the right leg September 15, 1940, resulting in amputation at right mid thigh September 18, 1940, due to gangrene of the right foot. These episodes were diagnosed as Buerger's disease.

On examination he appeared acutely ill, with a respiratory rate of 36, cold clammy skin and slightly cyanotic lips. There were numerous moist râles throughout the chest. The heart was enlarged 2 cm. outside the midclavicular line. There

were no thrills or murmurs. The rhythm was quite irregular, with a rate of 160. Blood pressure was 190/95 mm. of Hg. The abdomen was diffusely tender and slightly distended, but there were no palpable masses and no rigidity. He had had bilateral mid thigh amputations. Electrocardiogram confirmed impression of auricular fibrillation. Blood urea nitrogen was 34.9 mg. per cent; Kahn and Kline tests were positive; Wassermann, doubtful. He became progressively weaker and died within 24 hours of admission.

*Autopsy Findings:* The body was that of a 66 year old white male with both limbs amputated at mid thigh. The abdomen revealed all the small intestines to be markedly distended and discolored a bluish red, with the walls markedly thinned. No portion of the large intestine was distended, and no mechanical obstruction was present. There was an occlusion of the superior mesenteric artery by a firm grayish red clot about 6 cm. from its origin and distal to the origin of the right and middle colic arteries. On opening the abdominal aorta there was a firm grayish, dark red thrombus which completely occluded the aorta 0.5 cm. below the origin of the renal arteries. The thrombus was relatively firmly attached to the aortic wall and extended into the common iliac and external iliac arteries. In the iliac arteries the thrombus was very firm and fibrous in type and retracted from the vessel wall, so that a portion of the lumen still remained intact and was lined with smooth intima. The proximal portion of the abdominal aorta and thoracic aorta showed marked patchy atherosclerosis without ulceration of intima. The heart was enlarged, weighing 435 gm. The mitral orifice was constricted, admitting one finger. There was fusion of the mitral leaflets with verrucose vegetations, and the chordae tendineae were thickened and shortened. The coronary arteries showed focal patches of atherosclerosis and slight narrowing of the lumen in these areas. The right kidney was markedly contracted, weighing 95 gm. The capsule stripped with difficulty, leaving a finely granular surface. The cortex showed marked focal thinning.

*Comment:* The cause of death in this case was rheumatic valvular disease with congestive heart failure and paralytic ileus of the small intestine due to thrombosis of the superior mesenteric artery. Records of previous admissions at another hospital show there were lower extremity symptoms six months before amputation and two and a half years before death. Reëxamination of pathologic sections taken at the time of amputation revealed an artefact of the artery in which the artery had been everted. The histologic changes were those of atherosclerosis with patches of calcification, and there were no changes typical of thromboangiitis obliterans. The findings of an aortic thrombus, thrombosis of both iliacs, with manifest advanced canalization indicate a slowly progressive thrombotic process. Ulcerative atherosclerosis or syphilitic lesions were not present to account for the inception of the thrombus. The gradual onset of symptoms in the left leg makes it improbable that an embolism from the rheumatic heart was the etiologic factor.

*Case 6.* A 49 year old Negro male was admitted to Parkland Hospital February 7, 1945, with the complaint of difficulty in speech, pain and tenderness of both legs and feet, pain in left costovertebral angle and a convulsion. The speech difficulty, of four months' duration, was not one of articulation but of word aphasia. Three months before admission there was a gradual onset of pain in both legs and feet, intermittent in character but progressively worse. One week before admission there was a generalized convulsion lasting one hour, followed by left costovertebral angle pain.

Previous hospitalization history revealed that on April 26, 1940, the patient had begun to have cramps in the right big toe that extended into the calf of the leg and into the thigh. The pain was aggravated by cold weather and by standing or walking, and was worse at night. He had been previously admitted May 9, 1940, with a sudden pain and numbness of left arm, accompanied by blurring of vision, dizziness, profuse sweating and loss of consciousness. The left arm was pulseless and cool. On admission, blood pressure in the right arm was 114/86 mm. of Hg, and was not obtainable in the left arm. The left dorsalis pedis artery was not palpable. The condition had been diagnosed as scalenus anticus syndrome, and a left scalenotomy was performed, with very little improvement. At the time of discharge in 1940 blood pressure was 120/100 mm. of Hg in the right arm but was absent in the left arm. He returned to the hospital April, 1944, with complaint of headaches, vomiting and visual disturbances. Blood pressure was 150/100 mm. of Hg in the right arm, but absent in the left arm. The patient became symptom free on bed-rest, his blood pressure falling to 120/75 mm. of Hg. He was discharged with the diagnosis of hypertensive encephalopathy. Patient had had neurofibromatosis all his life.

Physical examination on his last admission revealed that the patient preferred to sit with his legs dependent. He had multiple soft tumors over his body. Blood pressure was 150/100 mm. of Hg in the right arm, but not obtainable in left arm. Neck veins were moderately distended. Pulsation could not be felt in the left radial artery or in the arteries of the lower extremities. The skin of the left forearm and both legs below the knees was cooler than the rest of the body. Laboratory findings were noncontributory. Blood pressure in the right arm reached as high as 210/140 mm. of Hg. On February 15, 1945, the patient developed a left hemiplegia, lost consciousness, became progressively weaker and died on February 17, 1945.

*Autopsy Findings:* The body was that of a slightly emaciated colored male about 50 years of age. There were numerous small tumor masses, polypoid in nature, projecting from the skin surface over most of the body. The first portion of the aorta appeared to be slightly dilated. On examination of the main branches of the transverse arch of the aorta, the following anomalies were noted: The first main branch from the arch consisted of a common artery which immediately bifurcated to give rise to the two common carotid arteries. The second branch came off about 0.5 cm. beyond the first and became the left subclavian artery. The third branch, immediately distal to the second, coursed posteriorly to the esophagus and became the right subclavian artery. Opening into the aorta showed a thrombus mass which was adherent to the left lateral and anterior walls of the aorta by fibrous adhesions. This thrombus was firm but friable. It had a grayish color with some mottled reddish areas. It was located in the upper portion of the ascending limb of the aorta, extending to and just barely beyond the point of origin of the first large branch from the aortic arch. A portion of the thrombus projected into the lumen of this first main branch and apparently occluded it. There was an open space between the thrombus and the posterior and right lateral walls of the aorta where blood apparently was able to course through the aortic arch. There was a moderate degree of arteriosclerosis noted in the aorta, most marked in the descending portion of the thoracic aorta, where atheromatous ulcerations were noted. There was an area of wrinkling and fibrous thickening of the intima in the left portion of the transverse arch. Dissection of the thrombus from its attachment showed no significant atheromatous plaques to be present in this region.

The heart appeared normal except for a 4 by 3 by 1 cm. thrombus in the left ventricle, which was gray, pale and very friable. There was some evidence of attachment to the heart wall by fibrous organization. There was no evidence of endocardial thickening or fibrosis. Thrombi were found in the small pulmonary artery branches. Examination of the splenic artery showed it to be occluded in the region of the hilus of the spleen by a soft red thrombus slightly attached to the vessel wall.



The central two-thirds of the spleen had become slightly liquefied and reddish gray. Opening the abdominal aorta revealed the distal 6 cm. to be completely occluded by a firm mottled reddish gray thrombus, which was attached to the lining of the aorta by fibrous tissue. The thrombus extended into both iliac arteries, completely occluding their lumen, and into the femoral arteries. Higher in the abdominal aorta, at the level of the celiac and superior mesenteric arteries, there was present a mural thrombus 2 cm. in diameter and 4 mm. in thickness, attached to the anterior wall with extension into the superior mesenteric artery, completely occluding the latter. The left suprarenal gland was greatly enlarged by a soft oval tumor mass which, on section, presented a gray mottled tumor surface. The right kidney weighed only 90 gm. The capsule was adherent. Section into the posterior part of the cerebral hemispheres showed on the left side a rather extensive area of softening and liquefaction.

*Microscopic Examination:* The aorta revealed thickened adventitia with mature fibrous tissue. The perivascular spaces contained numerous infiltrating lymphocytes and plasma cells. The endothelium of the vasa vasorum was swollen. There was slight diffuse and focal infiltration of the media with lymphocytes and scattered neutrophils. There was an unorganized fibrin and platelet thrombus attached to the intima. There were no sections of the thrombosed portion of the aorta. The heart revealed pericarditis, recent thrombosis and slight myocardial hypertrophy. The tumor mass in the left suprarenal gland showed the cellular structure of a histologically malignant paraganglioma. Sections of the brain showed microscopic evidence of multiple areas of encephalomalacia and degeneration of the myelin in the medulla. There were infarcts of the kidney and spleen. There were neurofibromata of the muscularis of the stomach and of the skin.

*Comment:* The cause of death was diffuse vascular disease resulting in multiple thrombosis of brain, heart, superior mesenteric artery and splenic artery, and at two distinct points in the aorta. This patient had symptoms of cramping of the right foot extending into the thigh, and absence of dorsalis pedis artery pulsation five years before death. Bilateral leg symptoms of gradual onset were noted three months prior to final admission. There is probably no relation between the symptoms of the left upper extremity in 1940 and the thrombus found in the ascending aorta; however, the symptoms in the lower extremities, extending for five years, may be related to the abdominal aortic thrombosis, and surely the gradual but definite leg symptoms of four months previous to death were caused by the abdominal thrombosis.

#### DISCUSSION

In this group of patients all were males, and the average age was 51 years. There were some variations in the manner of onset, ranging from such gradual appearance of symptoms that they could be dated only in terms of years, to the appearance of symptoms on a given date. In no case was the onset of dramatic nature. The duration of symptoms averaged six and three-tenths years. Three cases had intermittent claudication and two had excessive fatigability; in one case the history on this point was inconclusive. Sexual impotence was a presenting complaint in only one case. The absence of aortic pulsations in the abdomen was observed in two cases; how-



ever, three of the cases were not seen by us. An antemortem or clinical diagnosis was made in two cases.

The symptoms of occlusion of the aorta depend upon the rapidity of the development of the occlusive process. In a slow-forming thrombus of the terminal aorta, the process was of such gradual nature that collateral blood vessels were able to develop, and were in evidence or demonstrable by arteriogram in the first three cases. Also, the circulation to the lower extremities was sufficient to prevent the appearance of acute symptoms. In the remaining cases the occlusive process did not allow for development of sufficient collateral circulation, and there were varying degrees of acute circulatory inadequacy.

It is recognized that the symptoms of chronic thrombotic obliteration of the aorta are insidious and often complicated by more obvious disease processes; yet its clinical recognition is possible in cases that may be mistaken for coarctation of the aorta, or occlusive vascular disease of the lower extremities.

Treatment in none of the above reported cases was of a definitive character, due to the late stage of the disease at the time of diagnosis, or to the fact that a diagnosis was not made ante mortem.

#### SUMMARY

1. The literature on thrombosis and embolism of the aorta is reviewed.
2. Six cases of thrombotic obliteration of the abdominal aorta are reported, one case complicated by a large mural thrombus in the ascending aorta.
3. The clinical characteristics of gradual onset, unstable penile erection, extreme fatigability of lower extremities, absence of abdominal pulsation and trophic changes of extremities are discussed in relation to the above cases.

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## THE RÔLE OF THE ADRENAL IN HYPERTENSION \*

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THE relationship of the adrenal gland to essential hypertension in the hypertensive syndrome has been the subject of a vast amount of work and speculation at both the experimental and the clinical level. In spite of the enormous amount of data that has accumulated, this relationship is by no means clear at the present time. However, certain patterns relating the adrenal to the hypertensive syndrome have evolved and are of a good deal of interest to those who are following patients with hypertensive disease.

The pattern derived from work with laboratory animals begins with the observations of Goldblatt,<sup>1</sup> who found that total adrenalectomy interfered with the production and maintenance of experimental hypertension produced by placing clamps upon the renal arteries. Page<sup>2</sup> confirmed these observations a year later, although contradictory results were reported by another group of investigators.<sup>3</sup> Essentially the same observations as those of Goldblatt and Page were made by Collins and Wood,<sup>4</sup> who placed a slightly different interpretation upon it, however, maintaining that the adrenal was probably necessary for the maintenance of hypertension only as it was necessary for the maintenance of normotension. Since a hormonal agent, renin, had been implicated by these observers in the etiology of this type of hypertension, it is of interest to note that some workers report a decreased sensitivity to renin injections in the adrenalectomized animal, and that adrenalectomy has been reported to interfere with the production of a vasoexcitor principle produced by kidney tissue in *in vitro* anaerobic conditions,<sup>5</sup> an interference which can be reversed by the administration of desoxycorticosterone acetate. The work of Selye<sup>6,7</sup> in the production of vascular lesions in animals by large doses of desoxycorticosterone acetate is well known, and a number of other observers have noted increases in the blood pressure of dogs and rats maintained on DCA, a rise which is potentiated by sodium chloride administration. Interestingly enough, if such rats, made hypertensive with DCA, are allowed free choice of water and sodium chloride, they voluntarily decrease their sodium chloride intake.<sup>8</sup> This does not, however, seem to be universal knowledge among the hypertensive rat population, for the hypertensive animals reported by Braun-Menendez<sup>9</sup> actually increased their sodium chloride intake following the administration of DCA. While there is some question that desoxycorticosterone is identical with the salt retaining hormone elaborated by the adrenal cortex, and while the dosages

\* From the Symposium on Arterial Hypertension presented at the Thirty-third Annual Session of the American College of Physicians, Cleveland, Ohio, April 23, 1952.

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of this synthetic hormone employed by investigators may be criticized, the implication as to the relationship with the hypertensive syndrome is obvious. It is apparent that hypertension due to sodium and water retention under the influence of DCA might be expected, but there is evidence also that desoxycorticosterone-induced hypertension may persist in the rat following nephrectomy,<sup>10</sup> thus indicating that the action of this steroid must in part be independent of its effect upon the tubular handling of sodium and chloride.

Some of the experimental data in animals give us grounds for speculation about the relationship of the adrenal to the hypertensive syndrome in other types of so-called "renal hypertension." For instance, it has been shown that rats in which nephritis had been induced by cytotoxic serum respond with a striking hypertension to doses of DCA that produce no such effect in the non-nephritic animals.<sup>11</sup> When we realize that sodium depletion apparently stimulates the activity of the adrenal cortex, and that inability to conserve sodium is an early development in renal failure, these observations become of increasing importance. Furthermore, the renal lesion produced by acute choline deficiency is accompanied by marked hypertrophy of the zona glomerulosa of the adrenal cortex, the area believed to secrete salt-regulating hormones of the desoxycorticosterone type.<sup>12</sup> This is accompanied by a fall in the ratio of sodium to potassium in plasma despite absolute increases in both. It is known, too, that the severity of nephrotoxic globulin nephritis in the male rat is correlated with increase in adrenal weight<sup>13</sup> and, to complete the pattern, we must note the recent observations of the production of a syndrome closely resembling toxemia of pregnancy in rats with established DCA hypertensive disease which have been injected with renin.<sup>14</sup> It may be permissible to speculate further upon the fact that renin has been demonstrated to cause a marked increase in sodium and chloride excretion.<sup>15</sup> Such sodium and chloride losses might thus stimulate the adrenal, and it is tempting to try to relate these facts to the hypertension which so frequently complicates renal diseases. It is only fitting to conclude such a discussion of theoretical applications of experimental data with the fact that this renin-sodium relation does not obtain in the dog and has certainly not been demonstrated for the human.

The evidence for the relationship of the adrenal to hypertension drawn from observations at the clinical level is perhaps more pertinent but scarcely less speculative. The occurrence of hypotension in adrenal hypofunction (Addison's disease) and the frequent association of hypertension with adrenal hyperfunction (Cushing's disease) need no comment. The observation has been made that patients with so-called "essential hypertension" who develop adrenal insufficiency after the onset of their hypertensive syndrome may revert to normotensive levels. That patients with Addison's disease who have received excess amounts of desoxycorticosterone acetate may develop hypertension, even congestive failure, is also a well recognized clinical fact. That this hypertension and edema are associated with excess amounts of sodium, chloride and water is obvious. However, observations

have been made by others to substantiate the fact that such increase above normal limits in arterial pressure may occur in the course of treatment of Addison's disease apart from the phenomenon of abnormal sodium retention or increase in circulating blood volume,<sup>16</sup> thus again implicating an effect of adrenal cortical steroid-like substances, independent of their action on the kidney. Further evidence of this direct relationship has been adduced by Goldman and Schroeder,<sup>17</sup> who have demonstrated, in so-called "essential hypertensives," a pressor response to the intravenous administration of DCA not apparent in hypertension due to coarctation of the aorta. Our own experience with desoxycorticosterone glucoside has elicited such a result in only one of several patients tested.

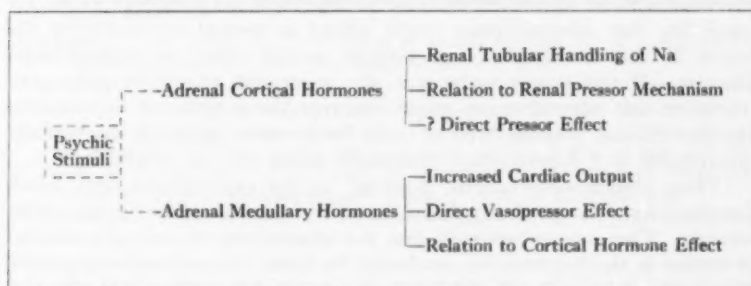
The rôle of drastic sodium restriction in the treatment of hypertension has been amply demonstrated by the use of rice diets and other low sodium diets in the human hypertensive syndrome. It is obvious that such drastic sodium restriction may play a part in hypertensive mechanisms other than those dependent purely upon body sodium and water depletion. The severity of the sodium restriction, the weeks or months it may take to achieve an effect, as well as the weight loss and protein deficiency which almost invariably occur on this régime, are all factors which eventually might lead to "adrenal exhaustion." There is suggestive evidence in human studies for this point of view. It should be pointed out, however, that since such patients continue to demonstrate marked urinary conservation of sodium, this effect, if it is a valid one, must be mediated through adrenal cortical steroids other than those associated with sodium metabolism. The fact that thiocyanate therapy, which has been used with some success in human hypertension, may be associated with a histologic picture of "adrenal exhaustion,"<sup>18</sup> and the fact that patients on rigid sodium restriction respond, as does the patient with Addison's disease, with a decreased tolerance to cholinergic drugs, are of additional interest.

In any discussion of hypertension, the psychic factor must bear considerable weight, and this is equally true when one attempts to assess the rôle of the adrenal in the hypertensive pattern. Obviously, psychic stress, anxiety and tensions may result in adrenal cortical responses. Even in the evaluation of rigid sodium restriction régimes, such as the rice diet, one must not forget that the conditions under which such patients are followed may constitute a form of psychotherapy difficult to divorce in its therapeutic significance from the effect of sodium restriction per se. The circumstances under which most of us live produce tensions and anxieties that must result in adrenal cortical activity. The tenets of our social structure, however, prevent the physical responses of running and fighting which were the primitive answer to such psychic stimuli. Therefore, this steroid outpouring may be thought of as being inadequately or inappropriately utilized, and the physical results comparable to the administration of exogenous steroid for which there has been no demand. The gastroenterologist is well aware of these relationships in the etiology of peptic ulcer, a syndrome in which both

psychic tension and adrenal cortical stimulation are known to produce exacerbations. It is perhaps permissible to see in this an analogy to Ingle's hypothesis that the "increased secretory activity of the adrenal cortex during stress goes to meet an increased need for the steroids and tends to maintain the status quo as far as the consequences of cortical hormone action are concerned."<sup>17, 19</sup>

Thus far, we have indulged in some speculative and, perhaps, philosophic thinking about the rôle of the adrenal cortex. We must not forget that the adrenal contains a medulla, and that products of this medulla are capable of producing hypertension. Epinephrine produces hypertension characterized mainly by an increase in cardiac output, while its demethylated analogue, nor-epinephrine, produces hypertension characterized by increased peripheral resistance which is, perhaps, more characteristic of the human hypertensive syndrome. Epinephrine per se may cause an increase in adrenal

TABLE I  
Participation of Adrenal Hormones in the Maintenance of Blood Pressure



cortical steroid production, and the experiments of Raab<sup>20</sup> have shown that the average pressor effects of both nor-epinephrine and epinephrine were significantly intensified after the administration of desoxycorticosterone acetate. These relationships are summarized in table 1.

From these data it appears that there exists a relationship between the adrenals and hypertensive vascular disease, although the exact delineation of this relationship to the clinical syndrome in humans is difficult to describe.

An approach to this problem has been made in the reports of previous workers who studied the effect of subtotal<sup>21</sup> and, in one instance, total bilateral adrenalectomy<sup>22</sup> on the hypertensive syndrome. In an accompanying paper in this journal,<sup>23</sup> the experience with 15 cases of bilateral total adrenalectomy followed for over one year is reported. Evaluation of these clinical results is difficult in many instances because the patients operated upon were chosen from a group with far advanced degenerative disease. In the patients with good results, an assay of the effect of the operative procedure



alone is also difficult, first, because nonspecific major operative procedures may cause amelioration of hypertensive vascular disease, and second, because in the patients reported by Wolferth,<sup>21</sup> subtotal adrenalectomy in several cases was combined with sympathectomy. In addition, one cannot eliminate the purely psychotherapeutic effect of prolonged hospitalization, and careful follow-up by an interested medical group. Such a regimen might well play a rôle in the therapy independent of the operative procedure. It seems apparent from the data reported so far that adrenalectomy, either total or subtotal, seldom accomplishes reversal of advanced vascular changes, particularly when associated with renal disease, if minimal replacement therapy is given with the steroids available today for therapeutic use. This fact has its experimental corollary in the observations that adrenalectomy does not abolish experimentally produced "kaolin hypertension" in dogs maintained on adrenal extract,<sup>22</sup> as well as the observations of the sensitivity of nephritic rats to DCA. The observation that it is possible for a hypertensive patient to respond to adrenalectomy with marked loss of edema, decrease in heart size and disappearance of protodiastolic gallop and pulsus alternans without significant decrease in arterial blood pressure<sup>23</sup> raises the possibility that adrenalectomy might afford a method of modifying the course of vascular disease even without specific effect on arterial blood pressure. If this proves to be true, the suggestion should be given consideration that adrenalectomy might interrupt the progress of hypertensive vascular disease, possibly even of renal involvement, although the vascular involvement and hypertension themselves might not be reversible.

These clinical observations, however, as the experimental ones which preceded them, do not clearly define the rôle of the adrenal in human hypertension. They suggest strongly that the adrenal may be one of a number of factors in the hypertensive syndrome, in some instances more important than others. It is possible, as has been suggested by other observers, that the quantitative interrelation of the adrenal steroids may be more important than the activity of the gland as a whole; that the ratio of one to the other of the corticoids might be a determining factor. The inadequacy of our ability to measure the excreted degradation products of the adrenal steroid and to relate them to their hormonal precursors at the present time does not allow us to confirm such speculations. Undoubtedly, however, the type of work here discussed will lead to further clarification of the etiologic and possibly the therapeutic aspects of the adrenal hypertension relationship.

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## CLINICAL STUDIES ON BILATERAL COMPLETE ADRENALECTOMY IN PATIENTS WITH SEVERE HYPERTENSIVE VASCULAR DISEASE\*

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### INTRODUCTION

THE aggravation of hypertensive cardiovascular disease which follows ACTH administration<sup>1,2</sup> lends support to the concept that amelioration of the vascular disease might follow a critical reduction in the function of the adrenal cortex. Further evidence in support of the thesis that the adrenal cortical secretions are involved in the maintenance of hypertension has been presented in another publication by one of us.<sup>3</sup>

The importance of the salt-retaining adrenal hormones in maintaining hypertension is suggested by the authors' experience in the treatment of hypertensive patients who subsequently have developed Addison's disease (figures 1 and 2). Under these circumstances a fall in blood pressure toward normal or even subnormal levels has been observed and further evidence of progressive vascular change has ceased. The administration of maintenance desoxycorticosterone acetate therapy has resulted in a restoration of the blood pressure to hypertensive levels and progression of the hypertensive vascular changes, whereas the administration of a maintenance dose of cortisone in combination with a minimal quantity of desoxycorticosterone acetate has restored a sense of well being and permitted the resumption of normal activities without restoration of severe hypertension. These observations suggest that if all adrenal cortical tissue could be removed from patients with hypertensive vascular disease and maintenance therapy provided with a favorable cortisone: desoxycorticosterone ratio, control of the hypertensive vascular disease might be accomplished in suitable cases.

Up to the present, complete surgical removal of the adrenals has not been justifiable because of the severity of the complications known to be associated with Addison's disease. However, the recent synthesis of cortisone, together with its relatively low cost and its efficacy when adminis-

\* Received for publication August 8, 1952.

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A preliminary report of this study was presented before the Association of American Physicians in Atlantic City, May 1, 1951, and was abstracted in *Tr. A. Am. Physicians* 64: 126, 1951.

A.T. ♂ 59 PRIOR TO 1939 - PROGRESSIVE HYPERTENSION

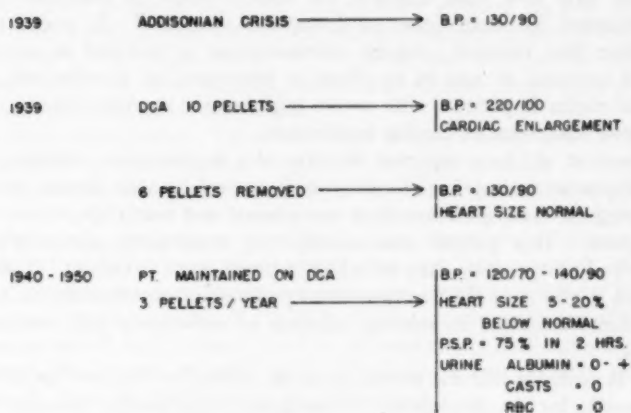


FIG. 1.

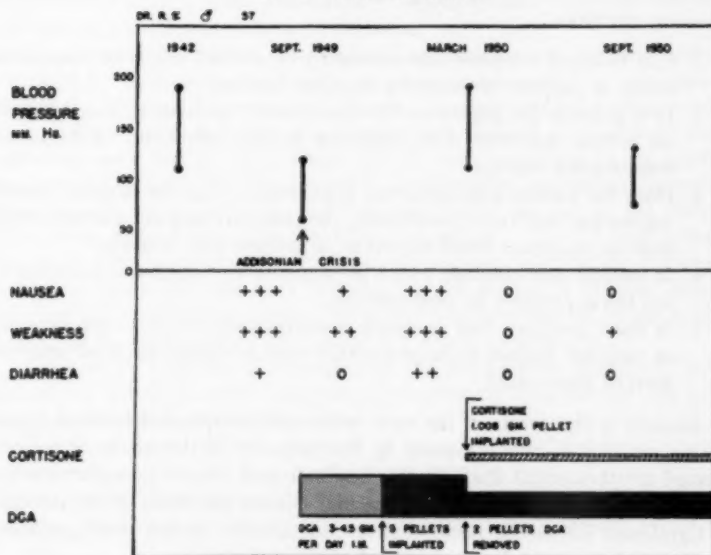
DEVELOPMENT OF ADDISON'S DISEASE  
IN A HYPERTENSIVE

FIG. 2.

tered orally, has made it possible to maintain in excellent general health a relatively large group of patients with Addison's disease. Many of these patients have now been followed for several years on cortisone therapy supplemented by small doses of desoxycorticosterone.<sup>4</sup> It would appear, therefore, that bilateral complete adrenalectomy is justified as an experimental approach in man in an effort to determine the possible rôle of the adrenal cortex in patients with severe hypertensive vascular disease, including those with renal or cardiac impairment.

Green et al.<sup>5</sup> have reported the case of a hypertensive, diabetic patient who appeared to improve clinically with respect to both disease processes following the complete removal of one adrenal and nearly all of the remaining gland. This patient was subsequently maintained successfully with a relatively large daily dose of whole adrenal cortical extract. Lukens et al.<sup>6</sup> and Wolferth et al.<sup>7</sup> have presented preliminary observations on a group of patients subjected to subtotal bilateral adrenalectomy with encouraging results.

It is probable that the secretions of the adrenal cortex are not primarily responsible for the development of malignant hypertensive vascular disease in most instances, but rather serve as an integral supporting mechanism involving the retention of sodium chloride and facilitating the development of hypertensive factors in the liver and kidney<sup>8</sup> and possibly augmenting vasoconstriction.<sup>9</sup> In the present study we have attempted to answer the following questions:

1. Can bilateral complete adrenalectomy be carried out with reasonable safety in patients with severe vascular disease?
2. Is it possible for patients with hypertensive vascular disease to carry on normal activities with cortisone as the only form of hormonal maintenance therapy?
3. Does the patient with advanced hypertensive vascular disease, including cardiac and renal insufficiency, respond to complete adrenalectomy with an excessive renal excretion of sodium and chloride?
4. Is sodium and chloride loss a prerequisite to substantial lowering of the blood pressure in such patients?
5. Is there evidence that complete adrenalectomy modifies the progress of vascular disease in respects other than a change in blood pressure level or heart size?

Because of the nature of the very severe and complicated form of hypertensive vascular disease presented by the majority of the group of patients selected for this initial study, many desirable and critical procedures either were not feasible because of the precarious clinical condition of the patients, or significant follow-up, postoperative comparative studies were precluded by the relatively early death of several of the patients.

## MATERIALS AND METHODS

Patients selected for study were admitted to the metabolic wards of the Peter Bent Brigham Hospital. They were allowed normal physical activity and a normal diet, except for sodium chloride intake, which was restricted to 1.5 to 2 gm. daily. A series of tests designed to establish base-line values of cardiovascular, renal and adrenal function was then performed under standard conditions.

*Cardiovascular Studies:* Values for blood pressure designated as "basal" were measured in the early morning before the patient arose. A sedation test, using amytal, was performed to determine blood pressure levels during sleep. A benzodioxane test<sup>10</sup> was performed routinely to investigate the possibility of pheochromocytoma. The cardiac status was evaluated with standard 7-foot heart films, electrocardiogram and measurement of vital capacity, venous pressure, and arm-to-tongue circulation time. Plasma volume was measured with T 1824.<sup>11</sup> Cardiac catheterization studies\* were performed in four patients prior to adrenalectomy, but because of the subsequent development of pulmonary infarctions in two of these patients (M. Ge., S. Ab.) this examination was abandoned.

*Renal Studies:* In addition to periodic routine urinalyses, serial modified Addis counts,<sup>12</sup> blood urea nitrogen levels,<sup>13</sup> phenolsulfonphthalein excretions and urea clearances were determined. Urine concentration and dilution tests were likewise obtained. Glomerular filtration was estimated with inulin<sup>14, 15</sup> or with sodium thiosulfate.<sup>16</sup> Renal plasma flow was measured with the para-amino-hippuric acid clearance.<sup>17</sup>

*Endocrinologic Studies:* The state of adrenal cortical function was ascertained by measuring the fall in circulating eosinophils in response to ACTH.<sup>18</sup> Urinary 17-ketosteroid<sup>19</sup> and 11-oxysteroid<sup>20</sup> excretions were determined before and during administration of ACTH as a 48-hour test.<sup>18</sup> Following operation an intravenous ACTH test, according to the method described by Renold, was performed.<sup>21</sup> Sodium and potassium concentrations in both serum and urine were measured with the use of the Barclay flame photometer, with an internal lithium standard. The salivary sodium:potassium ratio was measured serially in the manner described by Frawley.<sup>22</sup> Urine and serum chlorides were estimated by the technic of Schales, Schales and Asper.<sup>23, 24</sup> Changes in skin pigmentation were measured by the technic of reflectance spectrophotometry using the Hardy instrument.<sup>25</sup>

*Selection of Patients:* A summary of the preoperative status of the 15 patients on whom bilateral complete adrenalectomy was carried out more than one year ago is presented in table 1.

Eleven of these patients appeared to have advanced malignant hypertension, with systolic blood pressure levels ranging from 130 to 350 mm. Hg and diastolic blood pressure levels between 90 and 170 mm. Hg. Retinal changes, consisting of hemorrhages and exudates, were present in all but

\*The authors would like to thank Dr. Lewis Dexter for performing the cardiac catheterization studies in his laboratory at the Peter Bent Brigham Hospital.

one of these. Cardiac enlargement was observed in nine of this group. Frank cardiac decompensation had occurred in seven, and in three there was evidence of coronary artery disease. Pulmonary infarction from embolism had occurred in two following cardiac catheterization.

Three of the patients with advanced glomerulonephritis (J. Op., K. MacC. and J. Ma.) exhibited elevated blood pressure, marked renal insufficiency, vascular changes in the fundi and cardiac and hepatic enlargement; one patient with chronic glomerular nephritis (J. H.) had no cardiac involvement and only minimal eyeground changes, but both systolic and diastolic blood pressure was elevated.

TABLE I

Patient	Age	Sex	Duration of Hypertension	Basal Blood Pressure (mm. Hg)		Cardiac Enlargement % Normal	Blood Urea Nitrogen* (mg. %)	Glomerular Filtration (ml./min.)	Retinopathy†
				Minimum	Maximum				
M. Te.	52	M	6 years	160/100	350/150	—	29	17	3+
W. Co.	29	M	5 years	180/120	230/180	+25	13	113	3+
W. Ch.	34	M	10 years	150/120	180/140	+40	28	35	1+
C. Ha.	40	F	1 year	170/110	240/130	0	25	39	3+
S. Ab.	50	M	7 years	220/120	250/160	+40	19	72	4+
H. Ha.	26	M	1 year	130/90	230/160	0	18	80	4+
A. Ma.	38	F	6 years	210/120	242/140	+75	10	37	4+
E. McC.	42	M	11 years	198/120	260/170	+30	20	45	2+
M. Ge.	48	M	1 year	200/140	250/140	†	23	—	2+
K. MacC.	41	M	4 months	130/90	184/120	+22	28	20	3+
J. Op.	30	M	2 years	180/92	240/110	†	141	—	4+
J. Ma.	30	M	12 years	160/120	210/160	+27	61	15	4+
J. Ho.	40	F	2 years	170/100	190/120	0	10	73	1+
W. Mo.	37	M	6 years	194/140	290/178	+6	48	18	4+
E. Ga.	32	M	10 years	188/102	230/160	+27	28	112	4+

\* Average value for several determinations measured preoperatively.

† Retinopathy was graded as follows: 1+ = vessel narrowing and tortuosity only, with no disc changes; 2+ = moderate arteriosclerosis with old exudates; no recent hemorrhages; 3+ = advanced arteriolar change with scattered exudate, hemorrhages and blurring of disc margins; 4+ = widespread old and recent exudation, fresh hemorrhages and papilledema.

‡ Accurate estimation of heart size could not be made because of congestive failure.

*Preparation for Total Adrenalectomy:* Preoperatively, every effort was directed toward obtaining maximal circulatory efficiency by the use of a low-salt diet, digitalis therapy and mercurial diuretics when indicated. The duration of hospitalization prior to surgery was usually 10 to 20 days. In preparation for the operation, 100 mg. of cortisone acetate were given intramuscularly the night before and repeated the following morning two hours before surgery. During the operation, aqueous adrenal extract, in quantities up to 100 to 200 ml. in 5 per cent dextrose in water, was administered as a constant intravenous infusion to assure a high level of circulating hormone during the period of maximal stress. Phenylephrine hydrochloride USP (neo-synephrine) was administered intravenously as a constant infusion, the amount given being adjusted to prevent a fall in blood pressure below a level of 140/100 mm. Hg.

At the conclusion of the operation, cortisone, in a dose of 50 mg., was given every six hours for the first 48 hours and then gradually reduced to 25 mg. per day over a period of seven to 10 days. Neo-synephrine was employed during the first 24 to 48 hours following operation if blood pressure was not well maintained. Transfusions were administered in patients with preexisting anemia or to replace blood lost during operation. In patients without congestive failure, 250 to 500 ml. sodium chloride were given intravenously in the first 24 hours if blood pressure and circulatory status warranted it. All other parenteral fluid was *sodium chloride free*.

Since the completion of the series herein reported, one significant modification of the above program has been successfully employed in six additional patients undergoing complete adrenalectomy. Solutions of free cortisone and hydrocortisone (compound F) suitable for continuous intravenous administration have recently been prepared in this laboratory and demonstrated to exert highly potent metabolic and therapeutic effects.<sup>26</sup> Solutions of these pure corticosteroids, known to be important in the mediation of physiologic reactions mobilized under conditions of severe stress, have therefore been infused throughout the operative procedure and during the first four to eight hours of the immediate postoperative period. Dosage has been adjusted to an infusion rate of 10 to 12 mg. of hormone per hour, a level previously demonstrated to produce maximal metabolic changes and to be highly effective in the treatment of patients in adrenal crisis. This technic of administration would appear to be the method of choice in situations of acute and severe adrenal cortical hormone requirement.

The operative and immediately postoperative condition of the patients receiving cortisone or hydrocortisone infusions has been eminently satisfactory. It would appear from this small group that the cardiovascular stability of patients is increased, resulting in a material reduction in the requirements for vasoconstricting agents following operation.

*Operative Procedure:* The choice of anesthesia represents an important consideration in bilateral adrenalectomy in patients with hypertensive vascular disease. Intratracheal ether was used in the first three cases but was accompanied by marked fluctuations in blood pressure, especially during the induction phase and also during the postoperative recovery period. Continuous segmental spinal anesthesia was used in the most seriously ill patients, with excellent results.

The surgical approach most frequently used was through the bed of the twelfth rib after it had been resected, with the patient in the prone position.<sup>27-32</sup> The latter position permitted bilateral adrenalectomy without changing the drapes and operative field. For obese patients the posterolateral approach was considered desirable, with a complete change of drapes and position between operations on the two sides. A fall in blood pressure was anticipated whenever a significant change in position was made; hypotension was prevented or controlled by the use of neo-synephrine administered intravenously. Adequate exposure of the left adrenal was obtained



TABLE II  
Operative Summary

Patient	First Adrenalectomy	Postoperative Course	Second Adrenalectomy	Postoperative Course	Present Clinical Status	Diet	Added NaCl gm. q.d.	Cortisone mg. q.d.	DCA mg. q.d.
M. Te.	5/25/50	Transient hemiplegia	6/12/50	Severe angina and myocardial infarction; died 6/23/50 coronary occlusion	Dead	—	—	—	—
W. Co.	7/21/50	Transient right facial weakness	10/4/50	Uneventful	Greatly improved	Unrestricted	0	25	1.0
W. Ch.	7/26/50	Wound infection	11/15/50	Wound infection	Greatly improved	Unrestricted	0	25	0
K. MacC.	One-stage bilateral adrenalectomy		12/26/51	Uneventful	Unimproved	Low salt 1.5 gm.	0	25	0
J. Op.	12/19/50	Immediate but temporary improvement	12/28/50	Progressive uremia; coma	Dead	—	—	—	—
C. Ha.	One-stage bilateral adrenalectomy		1/12/51	Uneventful	Improved	Unrestricted	0	37.5	0.5
S. Ab.	One-stage bilateral adrenalectomy		1/13/51	Episode of adrenal insufficiency 2nd day	Improved	Unrestricted	0	37.5	0
H. Ha.	One-stage bilateral adrenalectomy		1/18/51	Tear of vena cava, required packing	Greatly improved	Unrestricted	0	25	1.0
J. Ma.	2/16/51	Uneventful	2/20/51	Sudden death on 12th postoperative day	Dead	—	—	—	—
A. Ma.	2/27/51	Distention, G.I. bleeding; epistaxis	4/3/51	Temporary psychosis	Unimproved	Unrestricted	1-3 occ.	25	0
M. Ge.	4/4/51	Uneventful	4/22/51	Died immediately post-operatively	Dead	Unrestricted	—	—	—
E. McC.	One-stage bilateral adrenalectomy		4/10/51	Uneventful. Died after 3 months	Dead	Unrestricted*	0*	25*	1.0*
J. H.	One-stage bilateral adrenalectomy		5/9/51	Uneventful	Improved	Unrestricted	6 gm. day	37.5	0
E. Gr.	6/19/51	Bilateral adrenalectomy		Died in uremia on July 14, 1951		—	—	—	—
W. M.	5/26/51	Bilateral adrenalectomy		Died in uremia on June 28, 1951		—	—	—	—

\* During three months following surgery.

through a posterior approach in all but the most heavily muscled male patients. The right adrenal lies higher than the left and is often more inaccessible because of the enlarged liver frequently encountered in patients with hypertensive cardiovascular disease. The right adrenal was dissected carefully from its position between the inferior mesial aspect of the liver and the vena cava. In two cases the right adrenal was found to lie over and around the vena cava, and in three it was actually embedded in a depression in the inferior surface of the liver. Care was taken to avoid injury of the renal vessels during retraction of the kidney inferiorly. On the left side, retraction superiorly was made with caution to avoid injury of peritoneum, splenic vessels and pleura; on the right, liver pleura and vena cava were similarly avoided. If the pleura was opened during the procedure, the contralateral adrenalectomy was deferred. The operative complications encountered in this study are listed in table 2.

*Postoperative Maintenance Therapy:* Within seven to 10 days following operation it was possible to place the majority of patients on maintenance hormone therapy. This consisted of 25 mg. of cortisone, injected once daily, and a diet of unrestricted sodium chloride intake. In some cases it was necessary to provide supplementary sodium chloride in tablet form in order to maintain an adequate salt balance. In a few patients it was necessary initially to administer a small supplement of desoxycorticosterone acetate, i.e., 0.5 to 1.5 mg. intramuscularly every 24 to 48 hours. When the patient's clinical status was well standardized, cortisone injections were replaced by orally administered cortisone. In most instances the same dose of hormone by mouth was substituted for that administered intramuscularly.

Cortisone by the intramuscular route was given once daily. Cortisone by mouth was given in the form of one-half tablet (12.5 mg.) twice daily before meals. Occasionally it was necessary to give a somewhat larger dose of cortisone by mouth, i.e., 37.5 mg. daily, to obtain an effect equivalent to 25 mg. given intramuscularly. During periods of stress or intercurrent infection, increased doses of cortisone, i.e., 50 to 100 mg. daily, and supplementary desoxycorticosterone acetate, 2 to 5 mg. daily, were administered until the patient's condition was well stabilized. In the presence of a gastrointestinal intolerance, the cortisone was always given intramuscularly.<sup>4</sup>

#### PATHOLOGIC OBSERVATIONS

*Studies on Adrenal Glands Removed at Operation:* Gross examination: The adrenals of 14 of the 15 patients did not appear to be grossly abnormal. There was no obvious hypertrophy or atrophy in any of the glands. In patient H. Ha. there was marked vascular congestion of both glands. In nine patients on whom postmortem examination was performed no evidence of accessory adrenal cortical tissue was discovered.

Microscopic examination of the adrenals removed at operation failed to reveal any histologic abnormality of cortex or medulla except in three

TABLE III  
Summary of Pathologic Findings on Kidneys

Patient	Gross Pathologic Changes	Microscopic Pathologic Changes	Diagnosis
M. Te.	Cortical surface granular, yellow; pale pink speckled cortex (autopsy)	Thickening of walls of afferent and efferent arterioles. Fibrosis of glomeruli (autopsy)	Arteriotar nephrosclerosis
W. Co.	Mottled surface, normal size (operative note)	Intimal fibrosis, proliferation in larger arteries. Scattered patches of fibrosis and chronic inflammation (biopsy)	Arteriosclerosis
W. Ch.	Granular surface; small kidneys (operative note)	Arteriosclerotic changes in large and small arteries. 20-30 per cent of glomeruli fibrosed (biopsy)	Arteriosclerosis
K. MacC.	Large, pale kidneys (operative note)	Diffuse and patchy lymphocytic infiltration. Tubular atrophy; rare fibrosis of glomerular tuft; no vascular changes (biopsy)	Chronic nephritis, possibly pyelonephritis
J. Op.	Left kidney absent; right kidney small, pale gray, cystic (autopsy)	Obliterated, fibrotic glomeruli; thickening of glomerular membrane; lymphocytic infiltration; increased fibrous tissue within parenchyma (autopsy)	Chronic glomerulonephritis
C. Ha.	Marked granularity and irregularity; ischemia (operative note)	Fibrosis of renal capsule and cortex (biopsy)	Chronic glomerulonephritis
S. Ab.	Left kidney: slight ischemia, smooth surface; right kidney: smooth surface, a few cortical cysts (operative note)	Biopsy unsatisfactory	—
H. Ha. J. Ma.	Normal in size and appearance (operative note) Double ureter on right; kidneys small and granular; cut surface flecked with tiny scars (autopsy)	Normal architecture (biopsy) Severe destruction of parenchyma; glomeruli fibrosed; proliferation of epithelium of Bowman's capsule (autopsy)	Normal kidney Chronic glomerulonephritis, arteriosclerosis
A. Ma. M. Ge.	Normal color and consistency (operative note) Normal sized kidneys; red, granular cortical surface (autopsy)	Biopsy unsatisfactory	Arteriosclerosis
E. McC.	Fine granular surface (operative note)	Medium and small arteries show walls thickened by fibrous tissue proliferation and hyalinization (autopsy)	Chronic glomerulonephritis
E. Gr.	Pale granular surface, left renal caliculi; numerous minute areas of hemorrhage (autopsy)	Many fibrous glomeruli filled with hyalin; glomerular capsular thickening and adhesions (biopsy)	Malignant nephrosclerosis
W. Mo.	Dark red, coarsely granular surface; small kidneys; cortex narrowed (autopsy)	Intimal hyalinization of arterioles, many glomeruli completely or partially hyalinized (autopsy) Marked distention of glomeruli, many fibrosed and hyalinized; necrosis of capillary tufts, intimal hyalinization of afferent arterioles (autopsy)	Arteriotar nephrosclerosis
J. Ho.	Kidneys pale brown, normal in size (biopsy)	Glomeruli scarred; possibly characteristic of Ellis's type 2 glomerulonephritis (biopsy)	Chronic glomerulonephritis

instances. The adrenals of patient H. Ha. showed marked congestion, those of patient A. Ma. showed hyalinization of the vessels of the capsule, and in patient E. Gr. there were degenerative changes in the zona fasciculata.

*Renal Pathology:* The posterior approach employed in these adrenalectomies provided an excellent opportunity to make a careful gross examination of both kidneys in all patients. Adequate renal biopsies were obtained from four of the five patients surviving. The gross anatomic changes and the microscopic diagnoses, as made on the biopsy material or by postmortem examination in nine of the 10 patients who succumbed, are summarized in table 3.

#### PHYSIOLOGIC OBSERVATIONS

*Studies of Adrenal Function:* During convalescence the response to intensive stimulation with ACTH was studied as an indication of the completeness of adrenalectomy (figure 3). Intravenous administration of ACTH under standardized conditions was the method employed,<sup>21</sup> since it has been shown that this induces an adrenal cortical response which is not significantly inhibited by the small doses of cortisone used for maintenance therapy. Changes in the level of circulating eosinophils and the urinary excretion of 17-ketosteroids were used as indicators of adrenal responsiveness. In evaluating the eosinophil response and the urinary excretion of 17-ketosteroids, careful consideration was given to the effect of the maintenance dose of cortisone therapy, since it has been shown that a prompt eosinophil fall may be observed after *oral* cortisone,<sup>22</sup> and that the quantity of 17-ketosteroids excreted with orally administered cortisone may be quite significant.

In two patients the right adrenal was adherent to the vena cava and meticulous dissection was required to insure complete adrenalectomy. In every other instance, however, it was possible at the time of operation to be certain that all traces of adrenal cortical tissue had been removed. Of nine patients who survived operation by more than one month, eight showed no evidence of adrenal activation during the eight hour intravenous ACTH test. One patient responded to the intravenous ACTH test with a 34 per cent fall in eosinophils. However, review of his therapy revealed that he had received 25 mg. of cortisone by mouth just prior to the infusion, which makes interpretation of the eosinophil fall controversial. This patient's 17-ketosteroid excretion showed no rise during the ACTH test. Postmortem examination of eight patients who died within a year of surgery revealed no residual or accessory adrenal cortical tissue. Even in a tenth patient who survived 13 months no adrenal tissue was found at autopsy. On one patient who succumbed three months after a satisfactory bilateral adrenalectomy, postmortem studies were not possible.

Skin pigmentation due to excessive melanin deposition is a prominent manifestation of chronic adrenal cortical insufficiency. The technic of reflectance spectrophotometry has been recently utilized in this laboratory

for the objective and quantitative measurement of changes in individual skin pigments which contribute to skin color in patients with Addison's disease and following complete bilateral adrenalectomy.<sup>34</sup> The changes encountered in the latter group are shown in figure 4. Following operation the entire reflectance curve becomes lower, which indicates a generalized darkening of the skin. Analysis of the curves in terms of component pigments reveals a depression in the near ultra-violet indicating the presence of "melanoid," a pigment considered to be a degradation product of melanin, and a flattening in the region 450 to 470 mμ due to a decreased content of blood in the tissues and to an increased proportion of reduced hemoglobin. These changes are more marked in areas with a high melanin content; indeed, the postoperative

#### POST-OPERATIVE RESPONSE TO ACTH

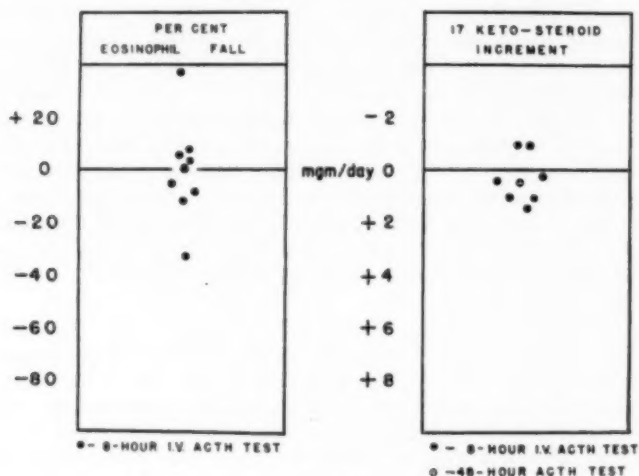


FIG. 3.

curve from a melanin-rich area bears a striking resemblance to that obtained with melanin itself.

The darkening detectable by visual examination of these patients was, with one exception, relatively slight. The high degree of sensitivity of the spectrophotometer undoubtedly explains the discrepancy between these findings and those of Huggins and Bergenstal,<sup>35</sup> who observed no significant increase in skin pigment after adrenalectomy. The decrease in pigmentation repeatedly observed in patients with Addison's disease after the institution of maintenance therapy with cortisone acetate may well indicate the mechanism whereby the majority of adrenalectomized patients continue to maintain a nearly normal skin color. For the latter patients, unlike those who spon-

taneously develop Addison's disease, are never permitted to become cortisone-deficient. Apparently, maintenance of normal or near-normal levels of circulating hormones of the 11,17-oxysteroid configuration inhibits the development of severe pigmentation.

*Subjective Response to Bilateral Adrenalectomy:* The majority of patients displayed a surprising sense of well being immediately following operation, which was attributed in part to the relatively large doses of cortisone

SPECTROPHOTOMETRIC RECORDINGS OF  
PIGMENT CHANGES IN MELANIN-RICH AND POOR  
AREAS FOLLOWING BILATERAL ADRENALECTOMY

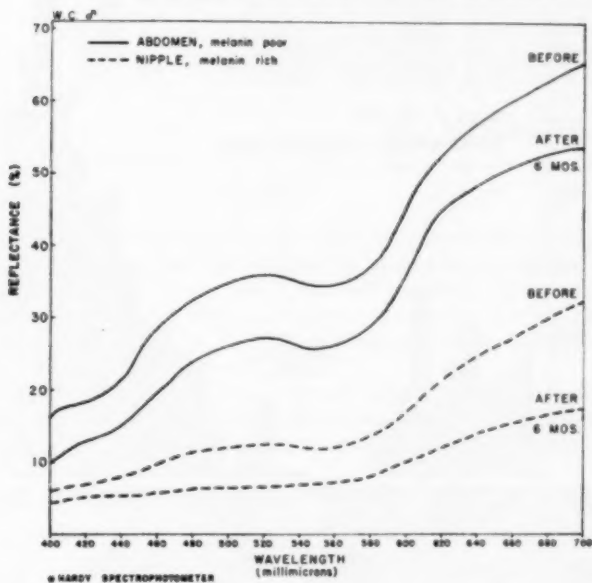


FIG. 4.

employed in the immediate postoperative period, and in part to the patient's realization that he had successfully survived a serious operation. One patient (A. Ma.) developed a frank psychosis, which persisted for approximately three weeks. This appeared to be related to marked alterations in electrolyte balance in conjunction with maintenance cortisone therapy and advanced cerebrovascular disease.

*Changes in Urinary Excretion of Electrolytes:* The most striking change which occurred during the postoperative period in all patients who survived

bilateral complete adrenalectomy was the magnitude of the increased renal excretion of sodium and chloride (figure 5). In most patients potassium excretion was reduced during the period of sodium chloride diuresis, and the serum electrolyte changes reflected the altered urinary excretion, i.e., marked hypochloremia, hyponatremia and moderate hyperkalemia.

Increased excretion of sodium and chloride in edematous patients continued following the disappearance of edema, although the magnitude of the daily loss decreased appreciably. As soon as practicable, patients were maintained on a diet containing the same quantity of sodium chloride as that

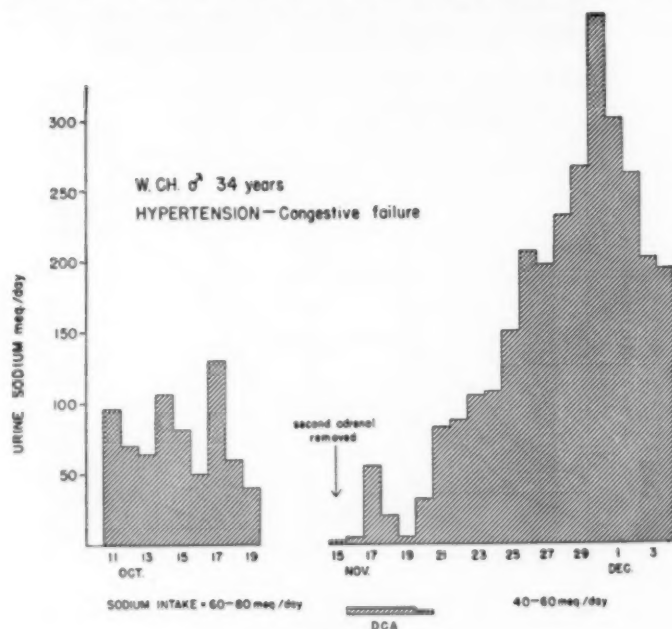


FIG. 5.

employed preoperatively, so that comparable studies could be made. An example of the magnitude of the sodium diuresis is presented in figure 6. The sodium chloride diuresis observed in these patients occurred despite maintenance cortisone therapy (usually 25 mg. daily). The sensitivity of these patients to salt-retaining adrenal cortical steroids is indicated by the prompt and marked reduction in sodium excretion which accompanied the institution of desoxycorticosterone replacement therapy (figure 6).

During the phase of increased sodium excretion, edema, when present, disappeared and heart size was reduced appreciably. Administration of



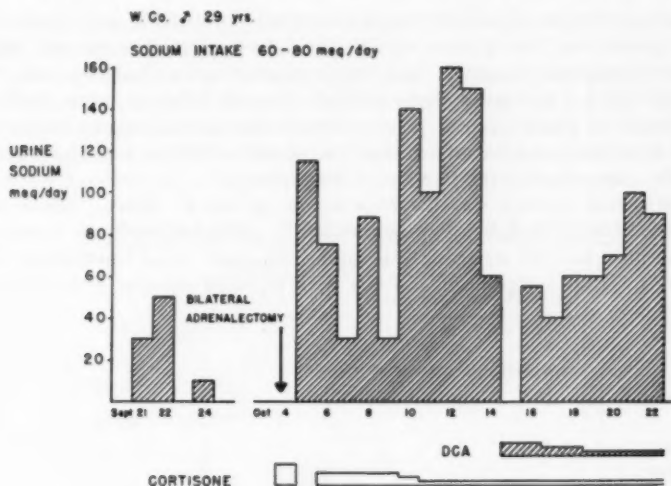


FIG. 6.

desoxycorticosterone restored the cardiomegaly of patient W. Co. (figure 7). In spite of the close correlation between the postoperative sodium chloride diuresis and reduction in heart size, there was frequently no significant fall in blood pressure. Exceptions to this statement occurred when rapid salt depletion exceeded ability of the body to maintain plasma volume and induced some degree of vascular collapse.

The extent of sodium diuresis immediately following operation was modified by the dose of supplementary hormone therapy and possibly by the vascular response of the patient during operation. An appreciable delay in

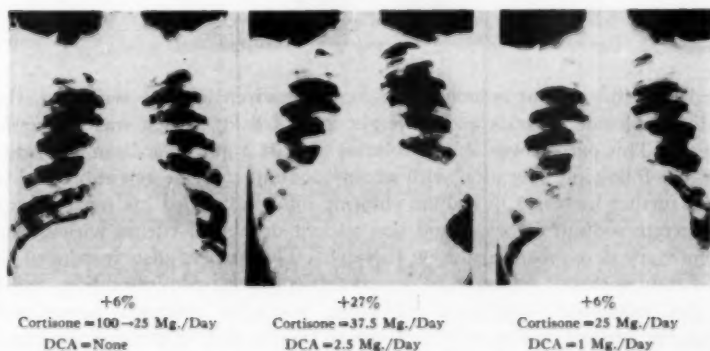


FIG. 7. Change in heart size in response to DCA therapy (W. Co., male, 29 years old).

the urinary output of sodium chloride occurred in patient S. Ab. (figure 8). This patient had had pulmonary infarcts before adrenalectomy and had a stormy postoperative course, with the development of a shocklike state, following which a marked sodium chloride diuresis failed to occur until the third week of convalescence. It is assumed that in this instance temporary renal functional impairment secondary to operative trauma and shock modified the expected response to adrenal insufficiency.

Of special interest was the response of patient K. MacC., whose pre-operative clinical course was characterized by a marked nephrotic syndrome complicated by mild azotemia. Despite high-grade renal involvement and failure to effect a significant diuresis with repeated courses of ACTH and

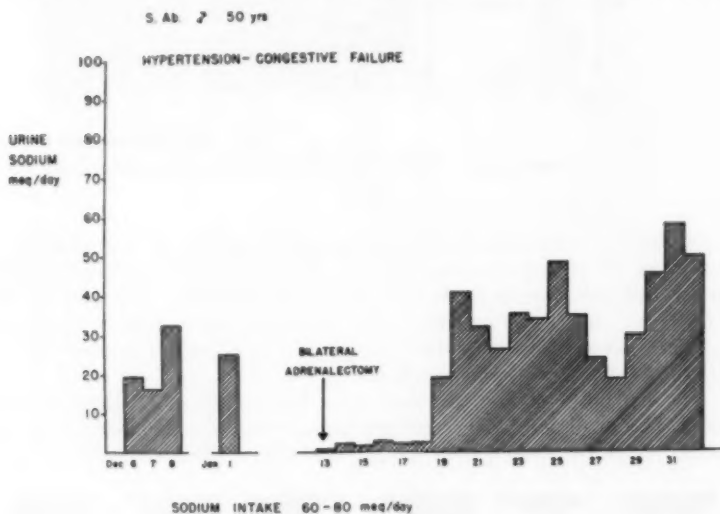


FIG. 8.

cortisone, this patient responded to complete adrenalectomy with a marked sodium chloride diuresis and a weight loss of 8 kg. which was not anticipated. This patient was able to tolerate at least 5 gm. of sodium chloride in his diet following operation without any sodium chloride retention. However, further increases in sodium chloride intake exceeded his renal capacity to excrete sodium chloride, and this patient developed edema without supplementary desoxycorticosterone therapy. This patient also responded immediately with salt retention to desoxycorticosterone administration, and all of his subjective symptoms, including headache, returned immediately. That the adrenal cortex may continue to secrete salt-retaining hormones in the late stage of chronic nephritis, despite edema and normal serum sodium

and chloride values, is suggested by the low Na:K ratio of saliva which has been detected under these circumstances.<sup>30</sup>

Careful observation of adrenalectomized hypertensive patients maintained on cortisone is necessary to avoid excessive sodium and chloride depletion, since the "euphoric effect" of cortisone may mask the initial sign of salt depletion. Marked weakness, apathy, muscle cramps and hemoconcentration developed with prolonged loss of sodium and chloride. Studies

### A COMPARISON OF COMPOUNDS B & E UPON URINE ELECTROLYTES

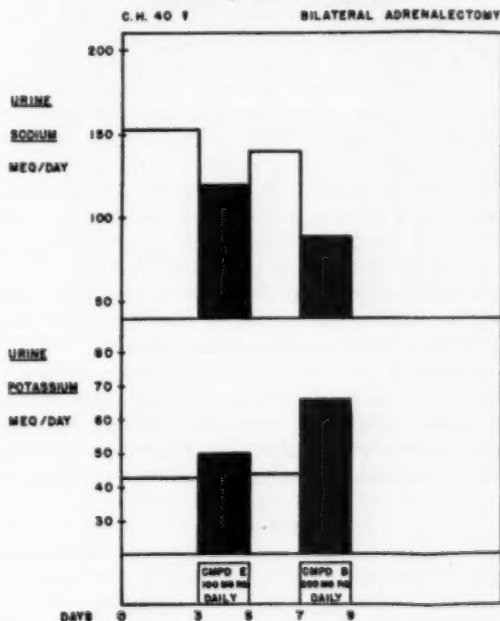


FIG. 9.

carried out for comparative purposes indicate that the salt retention resulting from the intramuscular injection of 100 mg. of cortisone daily was equivalent to that of 2.5 mg. of desoxycorticosterone. A comparison between the salt-retaining effects of Compounds B and E in a patient following bilateral complete adrenalectomy was carried out (figure 9).

Patient J. Ho., following complete adrenalectomy, while being maintained on 37.5 mg. cortisone daily and 6 gm. of supplementary sodium chloride, was tested with corticosterone (Compound B). Corticosterone

TABLE IV  
Serum Electrolyte Changes on Maintenance Cortisone Therapy with Inadequate  
Supplementary Sodium Chloride or Desoxycorticosterone Therapy

Patient	Months Post- operative	NaCl Intake gm./day	Cortisone Dose mg./day	DCA Dose mg./week	Blood Pressure mm. Hg	BUN mg. %	Serum K mEq./l.	Serum Na mEq./l.	Serum Cl mEq./l.
C. Ha.	9	10-12	37.5	3	200/140	39	7.0	131	108
A. Ma.	5	3	37.5	0	200/128	35	8.0	125	100
W. Ch.	9	ad lib.	25	0	152/100	35	7.5	136	106

was given by mouth in a daily dose of 50 to 100 mg. and subsequently by injection, 50 mg. daily. Both the oral corticosterone and the intramuscularly administered corticosterone induced weight gain, sodium and chloride retention, a marked elevation in blood pressure (to a level of 185/115), a return of symptoms of headache and fullness in the head. The cardiac diameter increased from 103 mm. (predicted diameter, 108 mm.) to 112 mm. (predicted diameter, 110 mm.). Fifty milligrams of corticosterone administered intramuscularly were more effective in this respect than 100 mg. of corticosterone given by mouth. Following the discontinuance of corticosterone, but while on a maintenance dose of cortisone and supplementary salt, the patient's blood pressure fell to the pre-treatment level of 145/110, the heart size subsequently returned to normal and the symptoms disappeared. These studies suggest that the addition of corticosterone above a maintenance dose of cortisone was capable of reproducing the clinical picture which existed prior to bilateral complete adrenalectomy.

With more prolonged periods of observation it has become evident that patients with advanced renal disease are predisposed to hyperkalemia, usually despite adequate urinary output, and most often with moderate depression of serum sodium and chloride levels (table 4). Restriction of potassium intake has proved helpful. In certain instances it has been necessary to give sup-

TABLE V  
Basal Blood Pressure Levels in Patients Following Bilateral Complete Adrenalectomy

Patient	Preoperative Blood Pressure (mm. Hg)	3 Months Postoperative Blood Pressure (mm. Hg)	6 Months Postoperative Blood Pressure (mm. Hg)	12 Months Postoperative Blood Pressure (mm. Hg)
W. Co.	160/100-350/150	128/98-140/188	124/98-140/104	—
W. Ch.	150/120-180/140	120/80-150/110	124/84-160/110	140/102-160/120
K. MacC.	130/90-184/120	150/80-184/118	160/90-200/150	150-90*
C. Ha.	170/110-240/130	150/100-200/110	180/130-200/130	160/130-225/160
S. Ab.	220/120-250/160	150/100-224/136	170/90-180/100	210/124-145/95†
H. Ha.	130/90-230/160	110/80-150/104	130/105	160/120†
A. Ma.	210/120-242/140	172/104-210/112	126/160-200/128	—
E. McC.	198/120-260/170	130/100-212/144	—	—
J. Ho.	130/92-168/108	150/100‡	118/78-138/88	142/90-172/100

\* Patient was terminal at this time.

† 15 months after surgery.

‡ This determination was not basal.

plementary desoxycorticosterone acetate in order to restore potassium levels to normal.

*Changes in Cardiovascular System: Basal blood pressure:* Change in basal blood pressure in the nine patients who survived three months or longer is summarized in table 5. Thus far, there has been definite improvement in two (W. Co. and H. Ha.) and temporary improvement in one (S. Ab.). Patient W. Co. in this group obtained marked improvement in blood pressure and relief of symptoms, with complete rehabilitation to work, until his sudden death from an acute coronary occlusion 11 months following operation. In three of the remaining six patients there has been marked symptomatic improvement, without significant change in the basal blood pressure level. E. McC., who had symptomatic improvement but no significant change in blood pressure, succumbed three months after surgery. It is to be noted that the period of survival after operation in these patients is still relatively short.

In those patients whose blood pressure has fallen in response to adrenalectomy it has been possible to restore the blood pressure toward the original hypertensive levels with desoxycorticosterone, occasionally even with small doses such as 2.5 mg. daily, or large supplements of sodium chloride (6 to 9 gm. daily), administered for only a few days, and in one patient in whom an adequate trial of corticosterone was administered a similar response was observed (see J. Ho.). For obvious reasons, neither of these procedures has been maintained for any prolonged period of time. Studies of this type suggest a qualitative relationship between the dose of desoxycorticosterone used and the amount of salt-retaining hormones secreted by the adrenals of these hypertensive patients preoperatively.

*Retinal changes:* The initial findings in the ocular fundi of the 15 patients undergoing bilateral adrenalectomy varied from spasm of the vessels, exudates and hemorrhages, to frank papilledema (table 1). In two patients (H. Ha. and E. McC.) the papilledema disappeared following operation. Patient K. MacC. (progressive chronic nephritis) not only failed to show any improvement in retinopathy following adrenalectomy, but actually showed progression of the retinal changes. Although the periods of observation are short, and although in the majority of instances a striking fall in blood pressure has not occurred, it is evident that, with the exception of patient K. MacC., the retinal changes have not progressed and in two instances have regressed significantly.

*Heart size:* The changes in heart size observed following bilateral complete adrenalectomy are illustrated in figure 10. The marked improvement observed in cardiac function and size following adrenalectomy would seem to indicate that hypertensive patients whose congestive failure is the chief cause of disability are more likely to obtain considerable improvement following operation. Corresponding improvement was observed in vital capacity, venous pressure and circulation time following the operation.

Measurement of the blood level of hypertensinogen and renin\* prior to and following operation has been carried out in five patients. Thus far a fall in the level of hypertensinogen has been observed in only one patient. It should be noted that all patients were on maintenance cortisone therapy, which has been shown to increase hypertensinogen in experimental animals.<sup>27</sup>

Cardiac catheterization studies were carried out in four patients preoperatively. Because of the occurrence of complicating pulmonary thrombosis, follow-up studies postoperatively were abandoned in view of the precarious cardiovascular status of this particular group of patients. For this reason a definitive statement regarding the effects of bilateral complete adrenalectomy on cardiac output, peripheral resistance, etc., cannot be made.

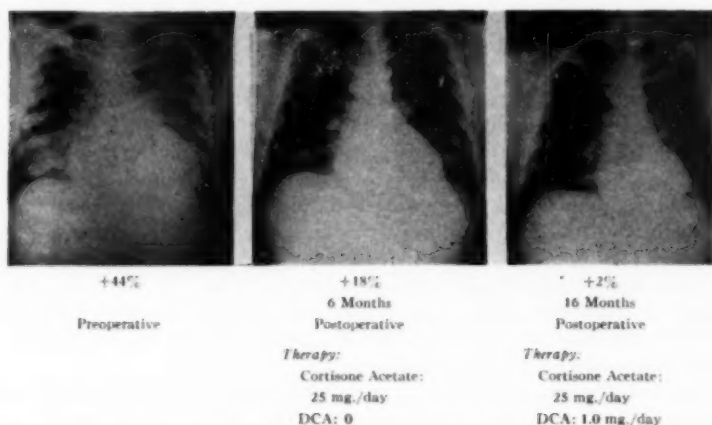


FIG. 10. Changes in heart size following bilateral adrenalectomy in hypertension (W. C., male, 36 years old).

One patient (W. Ch.) entered the hospital in congestive failure, with considerable cardiac enlargement and an accumulation of edema fluid in his legs. He also had a pulsus alternans and a gallop rhythm. During the two months following adrenalectomy his sodium chloride excretion increased dramatically. He lost all evidence of edema and the heart size returned almost to normal. At the end of this period the patient was not only ambulatory but also quite active. His pulsus alternans and gallop rhythm had disappeared.

*Changes in Renal Status:* Following operation 10 of the 14 patients in whom postoperative determinations were made showed a rise in blood urea nitrogen (BUN) the increment ranging from 10 to 20 mg. per 100 ml. In the five patients who died within approximately one month following surgery,

\*The authors wish to thank Dr. Florence Haynes for performing the hypertensinogen and renin studies in the laboratory of Dr. Lewis Dexter at Harvard Medical School.

the elevated nitrogen levels persisted or increased prior to death. In the nine patients who survived for longer than one month, five showed a rise in BUN following operation; of these, one has returned to preoperative levels, and in four patients the level has remained elevated or has increased. In the remaining four there was no significant change in BUN after operation. Phenolsulfonphthalein (PSP) excretion was measured in three patients preoperatively and postoperatively; in one, PSP excretion increased postoperatively and in the other two it remained unchanged. Addis counts done on this group of patients showed abnormally high numbers of red cells and casts in the urinary sediment. To date, no noteworthy changes have been observed in the quantitative urinary sediment constituents.

Renal function studies were done before and after operation in three patients. The results are shown in table 6. Some decrease in the clearance of inulin and para-aminohippurate (PAH) was noted, particularly in H.

TABLE VI  
Changes in Renal Function Following Bilateral Complete Adrenalectomy

Patient	Time	Inulin Clearance* ml./min.	PAH Clearance* ml./min.	Filtration Fraction ×100
C. Ha.	Preoperative	39	112	34.2
	7 months postoperative	30	87	29.5
H. Ha.	Preoperative	80	332	22.2
	7 months postoperative	52	272	19.0
J. Ho.	Preoperative	73	334	21.8
	5 months postoperative	76	352	21.6
	11 months postoperative	60	328	18.3

\* Results are the average of 4 or more clearance periods.  
Corrected for 1.73 M<sup>2</sup> surface area.

Ha., who had the greatest fall in blood pressure during surgery. Whether these changes were the result of progressing vascular disease or changes in vascular dynamics or were secondary to removal of the adrenals cannot be stated at this time. There is no doubt that a rise in BUN observed during the early postoperative period reflects the stress of surgery as well as the administration of large doses of cortisone. It will be important to determine over a longer follow-up period the effect upon renal function of loss of adrenal activity alone.

#### COMPLICATIONS

Operative complications included accidental opening of the pleura in three cases. An immediate closure was made and there was no difficulty from postoperative pneumothorax. In one patient, in whom the right adrenal was very adherent to the vena cava, the vein was injured and could not be sutured. Bleeding was adequately controlled by packing with Oxycel



and Gelfoam. Injury of the renal vein occurred in one case and minor wound infection in two cases. One patient with congestive failure died in the recovery room following cardiac arrest and hypotension which developed when he was transferred from the operating table to a bed in the recovery room. His operative chart had been stable throughout the operation as well as after operation until this occurred. It is now considered very important to permit patients to come out of anesthesia on the operating table, thus avoiding any change in position until they have regained consciousness and until the clinical chart has been stable for at least two hours. It has been customary to include antibiotic therapy during the postoperative period as a precaution against the development and spread of unrecognized infection which may occur during cortisone treatment.<sup>38</sup>

The possibility of psychotic episodes developing in patients who require large doses of cortisone<sup>2</sup> in their postoperative management must always be considered. Up to the present, this has occurred in only one of the 15 patients.

When the maintenance dose of cortisone is given by mouth, it is essential to appreciate the rapidity with which hormonal deficiency may develop when it is discontinued.<sup>33</sup> This is in contrast to the rate at which symptoms develop following the discontinuance of intramuscularly administered hormone.<sup>1</sup> Patients and relatives should be alerted to the fact that failure to take cortisone for a period as brief as 24 hours may precipitate a crisis, particularly in patients who are not receiving supplementary desoxycorticosterone acetate.<sup>4</sup> There is a delicate balance in which the adrenalectomized hypertensive patient is carried, due to efforts to minimize the steroid requirement, and therefore such patients are acutely susceptible to the withdrawal of hormone treatment. Failure of such patients to understand their increased need for adrenal steroids during periods of stress may result in a rapidly fatal crisis, such as occurred in one of the patients (E. McC.) three months following surgery.

Hyperkalemia always constitutes a risk in the patients with hypertensive vascular disease maintained on cortisone without desoxycorticosterone and with a minimal sodium chloride supplement. This fact is well illustrated in the values obtained in three patients who were being maintained on cortisone, either without desoxycorticosterone or with very small doses, in an effort to obtain maximal improvement in blood pressure and circulatory status. Under these circumstances an appreciable rise occurs in serum potassium level despite the maintenance of hypertension (table 4). It required supplementary sodium chloride, some reduction in dietary potassium intake, and desoxycorticosterone administered occasionally to correct this abnormality. Of the three patients shown in table 4, one subsequently succumbed, and the other two have continued to require desoxycorticosterone in relatively small dosage.

## DISCUSSION

Preliminary observations suggest that bilateral complete adrenalectomy is a feasible procedure in patients with advanced hypertensive disease. The majority of patients tolerated well the two-stage or single-stage operation carried out with adequate cortisone therapy. Following bilateral complete adrenalectomy the majority of patients were maintained in satisfactory hormonal balance with cortisone and supplementary sodium chloride medication. In general, the capacity of patients postoperatively to engage in normal activities of life correlated with the severity of their underlying vascular disease, with the exception of those rare instances in which weakness developed as a consequence of hyperkalemia secondary to sodium and chloride depletion.

The susceptibility of the adrenalectomized patient with hypertensive vascular disease to sudden withdrawal of maintenance hormonal therapy cannot be overemphasized. It is possible for fatal collapse to occur within a period as short as 48 hours. In this respect these individuals simulate patients with Addison's disease under hormonal therapy.

An increased capacity to excrete sodium and chloride was by far the most striking physiologic change observed in this group of patients. All patients who survived any appreciable period of time ultimately became "salt losers." True sodium diuresis was delayed for a period of three to four weeks in one patient in whom there was evidence of superimposed renal insufficiency (anoxic kidney) complicating the adrenalectomy. In several patients a delay in sodium diuresis appeared to be due to the large doses of cortisone employed postoperatively or, in certain instances, to supplementary desoxycorticosterone administered with a view toward preventing the rapid loss of sodium during the immediate postoperative period.

Although depletion of body sodium and chloride content appeared to be a prerequisite for a substantial lowering of blood pressure, rather appreciable losses of sodium were recorded in some patients without a significant change in basal blood pressure level. Following unregulated sodium diuresis, the transition from hypertensive blood pressure levels to shock occurred so rapidly in certain patients as to provide no opportunity for the maintenance of blood pressure within a normal range. As might have been anticipated, symptomatic improvement was observed following moderate depletion of sodium chloride in the absence of a significant depression of basal blood pressure level.

In this preliminary report it is not possible to explain the failure of certain patients to show a significant fall in blood pressure level. The status of renal function suggests itself as the most important single limiting factor. In general, there was a close parallelism between clinical improvement, change in blood pressure and status of renal function. Impression gained in this study suggests that it is inadvisable to perform a bilateral adrenalectomy on patients whose renal insufficiency has advanced to the point of

nitrogen retention. It also became evident that one of the principal points of concern in undertaking the operation was the prevention of further renal injury during the operative procedure. The precarious state of renal function in these patients is indicated by the low inulin clearance values observed in the majority of them (table 1). Every effort was made to prevent sudden changes in blood pressure during the operation and to minimize surgical trauma. So important did this seem to the authors that the advisability of concurrently denervating the renal artery was seriously considered. In at least one patient (J. Ma.), the rapid progression of uremia following operation suggested that the patient had sustained additional renal injury which resulted in progressive renal decompensation and an early death. There appears to be no doubt but that high-grade renal impairment seriously limits the overall benefits which may accrue from adrenalectomy, and that the preservation of renal function becomes the most important consideration during the operative procedure!

It is obvious in a study of this type that the important consideration is the evaluation of changes in the manifestation of hypertensive vascular disease, rather than changes in blood pressure per se. Improvement in retinal vascular changes appears to correlate closely with improvement in blood pressure, and certainly cardiac function may be expected to improve with significant reduction in blood pressure. Furthermore, the loss of excessive sodium chloride from the body may be of tremendous value in improving circulatory function in general. These improvements are all possible without appreciable changes in the underlying vascular disease. Whether adrenalectomy modifies significantly the progress of vascular disease in patients of this type will be extremely difficult to assess. That regression of changes already present will not be modified significantly is suggested by the postmortem findings in patient W. Co., who survived complete adrenalectomy for 11 months, with marked improvement in blood pressure and capacity to work, and who succumbed suddenly during working hours, having felt remarkably well up to the onset of his acute vascular accident. The coronary arteries in this patient revealed extensive atherosclerosis. Here one would be forced to assume that the marked functional improvement observed was the result of secondary changes (lowering of blood pressure and increased sodium and chloride excretion) rather than improvement in the underlying disease.

Another factor which merits consideration is the elimination of unpredictable cyclical fluctuations in the level of adrenal cortical activity which arbitrarily follow bilateral complete adrenalectomy. Thus, complete adrenalectomy may be considered to bring about two major changes in the adrenal hormone pattern: (1) a qualitative change in the nature of the circulating adrenal steroids, depending upon the type of substitution therapy selected, and (2) the elimination of unpredictable cyclical fluctuations in the level of circulating steroids.

It is evident from this study that if definitive evaluation of the rôle of the adrenal cortex in hypertensive vascular disease is to be made, it will be necessary to select, arbitrarily, a group of patients who do not present serious complications of the underlying vascular disease. In contrast, if one is interested in evaluating the therapeutic benefits to be derived from this procedure, more advanced cases of hypertensive vascular disease must of necessity be chosen.

#### CONCLUSIONS

1. Bilateral complete adrenalectomy, either single or double stage, is a feasible procedure in patients with advanced hypertensive vascular disease.
2. Renal impairment, with nitrogen retention, constitutes a contraindication to the operation, whereas the presence of congestive failure and progressive retinal vascular changes does not.
3. Every attempt should be made to minimize renal injury during the operative procedure.
4. Increased sodium and chloride loss is the most conspicuous physiologic change following operation.
5. Sudden reduction or withdrawal of adrenal hormone therapy can precipitate adrenal crisis in 24 to 48 hours in patients with vascular disease who have been maintained consistently on replacement therapy following operation.
6. The degree of activity attained by patients maintained on cortisone and supplementary sodium chloride therapy correlated with the persistence of hypertensive vascular complications rather than with alterations in adrenal function.
7. Although increased sodium and chloride excretion always preceded a significant fall in blood pressure late in convalescence, the loss of these electrolytes was not necessarily accompanied by a decrease in the level of basal blood pressure. Marked clinical improvement occurred in those patients who preoperatively presented evidence of excessive sodium and chloride retention.
8. It appears justifiable to explore further the usefulness of bilateral complete adrenalectomy in those patients with rapidly advancing malignant hypertension with reasonably adequate renal function who have failed to respond to conservative medical therapy.

#### CASE REPORTS

*Case 1 (W. Ch.)* This 34 year old white male laborer was known to have had hypertension for 10 years. Three months prior to hospitalization he developed swelling of the lower legs and accumulated abdominal fluid, and was troubled by episodes of paroxysmal nocturnal dyspnea. Initial physical examination showed a dusky white male in congestive failure, with an enlarged heart and a pulse rate of 110. Inspiratory basal râles, sacral edema, hepatomegaly and shifting dullness in the abdomen were present. The fundi showed arteriolar spasm but no hemorrhage or exudate. Basal blood pressure varied from 150/120 to 180/140 mm. of Hg. His

heart was enlarged plus 40 per cent. The venous pressure was 70 mm. of saline; arm-to-tongue circulation time, 35 seconds, and vital capacity, 3,000 c.c. (after digitalization and loss of 8 kg. in weight). Cardiac catheterization studies indicated both right and left ventricular failure. An amyltal sedation test lowered the blood pressure from 150/120 to 140/90 mm. of Hg. The electrocardiogram indicated left ventricular hypertrophy. The urine contained 1 to 4 plus albumin, and the sediment contained granular and hyaline casts, with a few white blood cells and no red blood cells. Phenolsulfonphthalein excretion was 55 per cent in two hours. The glomerular filtration rate was 34.8 c.c./min. (thiosulfate). Retrograde pyelography showed normal pelves and calyces, but the kidneys were reduced in size bilaterally. The adrenals were removed in two stages, each procedure complicated by wound infection. Postoperatively the urinary sodium excretion increased and the patient lost the remainder of his clinical edema, with reduction in heart size to plus 25 per cent, increase in vital capacity to 3,400 c.c. and disappearance of nocturnal dyspnea, hepatomegaly and pulmonary congestion.

Blood pressure has fallen to the range of 130/90 to 140/100 mm. of Hg. After one year the patient is ambulatory, very active and capable of working. Renal biopsy revealed atherosclerosis of small and large vessels, with fibrosis of 20 to 30 per cent of the glomeruli.

*Summary:* A 34 year old laborer with long standing hypertension and recent onset of congestive failure who has improved considerably following adrenalectomy.

*Case 2 (C. Ha.).* A 40 year old white single female office clerk had a four year history of hypertension, particularly severe for a year prior to admission. Restricted salt intake and sedation had failed to lower the blood pressure and, although no evidence of congestive failure or renal insufficiency had developed, the patient sought treatment for a subconjunctival hemorrhage and nausea and vomiting. Basal blood pressures were found to be 180/130 to 240/130 mm. of Hg. On physical examination the patient was found to have punctate exudates in the right fundus and an old hemorrhage in the left fundus, with AV nicking and tortuous arterioles. A pre-systolic gallop was present. The seven foot heart film was normal, and sedation with amyltal brought the blood pressure from 234/160 to 158/120 mm. of Hg. The blood urea nitrogen was 25 mg. per cent, and the phenolsulfonphthalein excretion in two hours was 20 per cent on one occasion and 40 per cent on another. The glomerular filtration rate was 31.5 to 37.3 c.c./min. (inulin) and renal plasma flow was 90 to 111 c.c./min. (PAH). Although the patient's symptoms of hypertension were few, the renal impairment contraindicated sympathectomy, and bilateral adrenalectomy was undertaken in one stage. Kidney biopsy showed fibrosis of the glomeruli. Following surgery, the urine sodium excretion increased. Azotemia temporarily worsened, with rise of blood urea nitrogen to 57 mg. per cent.

During the year postoperatively she has failed to show any change in the level of her blood pressure, but there has been no progression of vascular disease in the fundi and her heart size has decreased. She requires 0.2 mg. of Percorten weekly, in addition to supplementary salt in her diet to prevent muscle cramps, nausea and weakness.

*Summary:* A 40 year old white female with no cardiac damage but marked renal impairment bordering on azotemia, in whom bilateral adrenalectomy increased urinary sodium output and led to reduction in heart size but failed to lower blood pressure.

*Case 3 (J. Ma.).* The patient was a 30 year old tree warden with a 12 year history of hypertension and albuminuria. He complained of occipital and frontal headaches, blurring of vision, ankle swelling and exertional dyspnea for four months prior to hospitalization. Initial examination showed pallor of skin, uriferous breath, bilateral papilledema with retinal hemorrhages recent and old, cardiac enlargement with protodiastolic gallop, moist râles at both lung bases and pitting edema of the

lower legs. The basal blood pressure ranged from 160/120 to 210/160 mm. of Hg. A seven foot heart film revealed 16 to 27 per cent cardiac enlargement. Vital capacity was 4,500 c.c.; venous pressure, 150 mm. of saline; and arm-to-tongue circulation time, 16 seconds (after digitalization). Amytal sedation was followed by a fall in blood pressure from 170/120 to 150/100 mm. of Hg. Urinalysis showed 1 to 3 plus albuminuria, with occasional red cells and 1 to 2 granular casts per high power field. Blood urea nitrogen was 64 mg. per cent. Phenolsulfonphthalein excretion was 25 per cent in two hours. Glomerular filtration rate varied from 14.5 to 16.5 c.c./min. (inulin), and renal plasma flow was in the range of 57 to 65 c.c./min. (PAH). A serum lipoprotein (Sf 12-20) analysis showed 83 mg. per cent. Electrocardiogram showed left ventricular hypertrophy, and both the Master's test and ballistocardiogram were markedly abnormal. Urinary sodium excretion ranged from 30 to 50 mEq. per day on a 1.5 gm. sodium chloride diet. Bilateral adrenalectomy was performed in two stages. Renal biopsy showed chronic glomerular nephritis; both adrenals were normal histologically. On a postoperative diet of 3 gm. of sodium chloride, urinary sodium excretion was 25 to 65 mEq. per day. The blood urea nitrogen rose to 99 mg. per cent following surgery. There was no significant fall in basal blood pressure. On the twelfth postoperative day the patient died suddenly, having complained only of slight dizziness immediately beforehand. Postmortem examination failed to reveal the cause of death.

*Summary:* A severely hypertensive young white male with advanced retinal changes, congestive heart failure and renal failure who died suddenly on his twelfth day postadrenalectomy.

*Case 4 (A. Ma.).* This patient, a 38 year old white housewife, was known to have had hypertension six years before entry. She had been disturbed chiefly by severe headaches for one year, and had more recently developed blurring of vision, fatigue and exertional dyspnea. A low sodium diet, rice diet and protoveratrine administration produced only temporary benefit. Physical examination revealed a chronically ill woman with severe retinopathy, papilledema, white patchy exudates and flame-shaped hemorrhages. The heart was enlarged 1 cm. to the left of the midclavicular line. The lung fields were clear and the liver was not enlarged. The basal blood pressure ranged from 210/120 to 242/140 mm. of Hg. The heart x-ray showed 75 per cent enlargement. Vital capacity was 1,200 c.c.; venous pressure, 75 mm. of saline; and circulation time, 23 seconds. Electrocardiogram showed left ventricular hypertrophy. The blood urea nitrogen ranged from 10 to 20 mg. per cent. The urine contained 1 to 3 plus protein, with a negative sediment. Glomerular filtration rate was 37 c.c./min. (inulin), and renal plasma flow was 185 c.c./min. (PAH). The basal metabolic rate was plus 40 per cent, and the  $I^{131}$  uptake was 56.6 per cent in 24 hours. Therapy with  $I^{131}$  was carried out without subsequent change in the course of the hypertensive disease. A bilateral adrenalectomy was performed in two stages and each was followed by a slow convalescence. During recovery from the second procedure the patient manifested psychotic changes, with disorientation and attendant difficulty in management of her diet and hormone replacement therapy. The adrenals were normal histologically, aside from hyalinization of the arterioles in the capsule. She survived for six months following surgery, during which time her electrolyte and fluid balance was regulated with difficulty. Terminally she showed congestive failure, with accumulation of edema fluid despite a low salt diet. Her electrocardiogram just prior to death showed signs of potassium intoxication.

*Summary:* A 38 year old housewife with severe retinopathy, cardiomegaly and reduced renal function who developed a psychosis following adrenalectomy and died with congestive failure and hyperkalemia.

*Case 5 (H. Ha.).* This 26 year old salesman had a long standing history of intermittent albuminuria and a six-month history of rapidly progressive hypertension



with complications of substernal "heaviness," fatigue and headaches. No previous episodes of kidney disease were recognized. Initial examination revealed a nervous, heavy-set white male. Fundi showed bilateral papilledema, with white exudates and scattered flame-shaped hemorrhages. Lungs were clear. The heart was normal in size, with regular rhythm, and the pulse was 66. The basal blood pressure ranged from 130/90 to 230/150 mm. of Hg. A seven-foot x-ray showed no cardiac enlargement. The vital capacity was 4,200 c.c.; circulation time, 16 seconds; and venous pressure, 80 mm. of saline. Sedation with amytal lowered the blood pressure from 200/140 to 140/100 mm. of Hg. Electrocardiogram showed left ventricular hypertrophy. Urine contained 1 plus albumin with no cells or casts. Two-hour phenol-sulfonphthalein excretion was 85 per cent. On dehydration, the urine concentrated to 1.024. The glomerular filtration rate was 82 to 98 c.c./min. (inulin), and the renal plasma flow was 345 to 415 c.c./min. (PAH). The blood urea nitrogen varied from 18 to 23 mg. per cent. Both adrenals were removed at one stage, surgery being complicated by a tear in the inferior vena cava. Renal biopsy showed no pathologic changes. During convalescence the blood pressure dropped to the range of 110/82 to 140/100 mm. of Hg.

At the end of 18 months the patient's blood pressure is 160/120 mm. of Hg. as measured during an office examination, and the eye grounds show no papilledema and no hemorrhages or exudates. The blood urea nitrogen is 18 mg. per cent, but the urine contains 4 plus albumin. The glomerular filtration rate and renal plasma flow have decreased. The patient is free of symptoms, however, and pursuing his studies for a Master's degree in Education.

*Summary:* A 26 year old white male with rapidly progressive hypertensive vascular disease involving chiefly the fundi, who at first responded to adrenalectomy with a drop in blood pressure to near normal levels. At the end of 18 months his blood pressure remains elevated and renal function has diminished. The fundi remain improved.

*Case 6 (S. Ab.).* A 50 year old white male business executive had a seven-year history of hypertension and six year history of exertional dyspnea, headaches and orthopnea. Salt-free and rice diet, sedation and protoveratrine failed to achieve improvement. One year before entry the patient developed auricular fibrillation and required medication with digitoxin and quinidine. Episodes interpreted as angina pectoris had developed in the two months preceding admission. On physical examination the patient was found to be tense, perspiring and flushed. There were recent hemorrhages in both fundi with papilledema. The heart was enlarged 3 cm. to the left, and a definite protodiastolic gallop rhythm was heard. The rhythm was regular. A pulsus alternans was present. The liver was enlarged, but there was no peripheral edema. The basal blood pressures ranged from 218/120 to 280/180 mm. of Hg. A seven-foot heart roentgenogram showed plus 25 to plus 40 per cent enlargement. The vital capacity was 2,600 c.c.; the venous pressure, 240 mm. of saline; and the circulation time, 30 seconds (patient digitalized). A sedation test showed a drop in blood pressure from 240/144 to 160/120 mm. of Hg. Electrocardiogram showed left ventricular hypertrophy. The blood urea nitrogen was 16 mg. per cent. Phenol-sulfonphthalein excretion was 80 per cent in two hours. The urine concentrated to 1.022, and there was 1 plus albuminuria, with granular casts and a rare red blood cell in the sediment. The glomerular filtration rate was 72.7 c.c. per minute (thiosulfate). A bilateral adrenalectomy was carried out in one stage. The postoperative course was complicated by transient adrenal insufficiency with pulmonary atelectasis. Postoperative blood pressures ranged from 160/94 to 254/108 mm. of Hg, and urinary sodium excretion rose only slightly. Heart size fell to 15 per cent.

Throughout the year since adrenalectomy he has had difficulty in controlling electrolyte balance, with several episodes of weakness. His blood pressure fell some-



what after six months, but at the end of a year still remains elevated. He has had no further episodes of congestive failure or angina, but 18 months following adrenalectomy he was admitted to the hospital with hemiplegia following a cerebrovascular accident, from which he seems to be recovering well.

*Summary:* A 50 year old white male with long standing hypertension, congestive failure, angina pectoris, moderately severe retinal changes, good kidney function with no significant changes following adrenalectomy other than an increased renal excretion of sodium and improvement in the congestive failure. At 18 months following surgery he had a cerebrovascular accident, from which he appears to be recovering well.

*Case 7 (J. Ho.).* A 44 year old housewife was known to have had chronic glomerulonephritis for six years, with hypertension present for at least two years. She received some benefit from a rice diet. Just prior to adrenalectomy she was free of symptoms except for an occasional occipital headache. There was no history of congestive failure. There were no changes in the fundi except for slight A-V nicking. At the time of examination her blood pressure ranged from 180/100 to 190/120 mm. of Hg. There was no cardiac enlargement. She had a glomerular filtration rate of 73 c.c. per minute and a renal plasma flow of 334 c.c. per minute. The blood urea nitrogen averaged 15 mg. per cent. A one-stage bilateral adrenalectomy was performed on May 9, 1951. She recovered from the surgery without complications and did well on a program of 37.5 mg. of cortisone and small doses of Percorten.

During the year following surgery she has continued to feel well. Her blood pressure remains slightly elevated, in the range of 142/90 to 172/100 mm. of Hg. There have been no further changes in the eye grounds. The heart is not enlarged, but there has been some decrease in renal function, the glomerular filtration rate falling to 60 and renal plasma flow to 324.

*Summary:* A 44 year old woman with a six year history of chronic glomerulonephritis who had entered the hypertensive phase of the disease. There was no evidence of congestive failure. Eye grounds showed only minimal changes; renal function was reduced. Following adrenalectomy there has been little change in her status except for slight further reduction in renal function.

*Case 8 (M. Te.).* This 52 year old Jewish male entered with a six year history of severe hypertension. During the eight months before hospitalization he had developed congestive heart failure and progressive renal insufficiency. His basal blood pressures ranged between 160/100 and 250/150 mm. of Hg. The fundi showed narrowing and spasm of arterioles bilaterally, with exudate and hemorrhages on the right. The heart was markedly enlarged to the left, apical rate 60, with a grade II apical systolic murmur. The vital capacity was 2,600 c.c.; venous pressure, 85 mm.; and arm-to-tongue circulation time, 16 seconds (after digitalization). Electrocardiogram showed left ventricular hypertrophy. An amyltal sedation test caused a fall in blood pressure from 238/140 to 160/92 mm. of Hg. Cardiac catheterization studies showed low reserve in the left ventricle on exercise. Phenolsulfonphthalein excretion was 20 per cent in two hours. Blood urea nitrogen ranged from 24 to 38 mg. per cent. Urinalyses showed 3 plus albuminuria with fixed specific gravity (1.006 to 1.012). The urinary sediment contained occasional red cells with rare granular casts. Glomerular filtration rate was 16.6 c.c./min. (thiosulfate).

The patient had been refused as a candidate for sympathectomy, and therapy with sedation, low salt diet and thiocyanate had failed to arrest progress. A two-stage bilateral complete adrenalectomy was performed, the first procedure being complicated postoperatively by a transient left hemiplegia. Following removal of the second gland, the patient had several episodes of severe, crushing chest pain, with a terminal myocardial infarction occurring on the twelfth postoperative day. Post-mortem examination revealed an anteroapical myocardial infarct. Both adrenal glands were histologically normal. The kidneys showed arteriolar-nephrosclerosis.

*Summary:* A 52 year old male with congestive failure, arteriosclerosis and renal insufficiency who had a fatal coronary occlusion on the twelfth day following removal of his second adrenal.

*Case 9 (E. McC.).* This 42 year old unmarried male railroad clerk entered the hospital with a 10 year history of hypertension and albuminuria. He had had exertional dyspnea and nocturia for five years, and periodic headaches, morning vomiting and a sudden onset of diplopia and blurring of vision shortly prior to admission. On physical examination he was a thin, ruddy faced white male with poor muscle tone. He had an internal strabismus of the right eye, with diplopia on right lateral gaze. There were papilledema with arteriolar spasm and scattered patches of punctate white exudate and flame-shaped hemorrhages in the eye grounds. The heart was enlarged to the left, with a grade III apical systolic murmur and a loud A<sub>2</sub>. There was no edema. The basal blood pressure ranged from 198/120 to 260/170 mm. of Hg. An electrocardiogram showed development of characteristic left ventricular hypertrophy during hospitalization. The vital capacity was 3,100 c.c. and the heart size was 30 per cent enlarged. The two hour phenolsulfonphthalein excretion was 20 per cent on one occasion and 40 per cent on another. The glomerular filtration rate was 40 c.c./min. (inulin) and the blood urea nitrogen ranged from 18 to 36 mg. per 100 c.c. The patient underwent removal of both adrenals in one operation and his postoperative course was uneventful. The adrenals were normal histologically, the kidneys being small and granular, with a biopsy showing evidence of chronic glomerular nephritis. By the ninth postoperative week his blood pressure had fallen to 180/110 mm. of Hg, and symptoms of headache, blurring of vision, exertional dyspnea and diplopia had improved markedly. During the thirteenth postoperative week, while on a strenuous trip to another city, he became weak and dehydrated and had a marked fall in blood pressure with collapse. He died in an ambulance en route to the hospital.

*Summary:* A 42 year old white male with long-standing hypertension, with recent onset of visual loss, early congestive failure and biopsy evidence of chronic glomerular nephritis without renal failure clinically, who showed symptomatic improvement in the short time following surgery but died in shock following dehydration.

*Case 10 (M. Ga.).* This 47 year old white male widowed truck driver entered with an 11 month story of exertional dyspnea and a more recent history of headaches, substernal pressure, nocturnal dyspnea, memory loss, blurring of vision and hematuria. On physical examination he was short of breath and there was papilledema with arteriolosclerosis and profuse flame-shaped hemorrhages in the ocular fundi. He had engorgement of neck and arm veins, dullness and decreased breath sounds at both lung bases, and marked cardiac enlargement with protodiastolic gallop rhythm. The liver edge was down three fingerbreadths and there was 3 plus pitting edema of the lower legs. The basal blood pressure ranged from 200/140 to 250/140 mm. of Hg. A sedation test with amytal caused a fall in blood pressure to 200/120 mm. of Hg. The electrocardiogram showed no specific abnormalities. His vital capacity was 2,000 c.c. Venous pressure was 80 mm. saline, and the arm-to-tongue circulation time was 31 seconds. The phenolsulfonphthalein excretion was 50 per cent in two hours. The blood urea nitrogen ranged from 19 to 28 mg. per 100 c.c. after bed-rest and administration of mercurial diuretics. The urine contained 1 to 3 plus protein and hyaline casts. Following improvement of congestive failure, he was subjected to a two-stage bilateral adrenalectomy. Although he seemed to have tolerated well the removal of the second adrenal, he died immediately postoperatively due to cardiac arrest. Postmortem examination showed no evidence of pulmonary embolism or myocardial infarction, and definite cause of death could not be established pathologically.

*Summary:* A hypertensive male with severe retinopathy and congestive heart failure who died suddenly following the removal of his second adrenal gland.

*Case 11 (J. Op.).* This patient was a 29 year old single white male business executive with a 12 year history of pyelonephritis in a unilateral fused kidney. Six years prior to admission his renal function was known to be markedly reduced, but he was normotensive. During the year prior to entry, however, blood pressure rose to hypertensive levels and he became uremic during the three months prior to entry. On admission he was found to be a pale, edematous, partially blind, severely ill white male with a uremic breath. Blood pressure ranged from 180/92 to 240/110 mm. of Hg. Periorbital edema and bilateral subconjunctival hemorrhages were present. Fundi contained numerous flame-shaped hemorrhages. There were moist râles at both bases. Heart was enlarged to the left, with a grade III apical and pulmonic systolic murmur, and protodiastolic gallop rhythm. The heart rate was 100; circulation time, 16 seconds; venous pressure, 150 mm. The vital capacity was 2,900 c.c. The blood urea nitrogen was 95 mg. per cent. The urine contained 3 plus albumin, with 12 to 15 red blood cells per high power field. The patient was considered to be in terminal uremia with severe hypertension on the basis of a chronic pyelonephritis in a unilateral fused kidney. Bilateral adrenalectomy was undertaken in the hope of arresting the course of the hypertensive disease. The patient was prepared for surgery by hemodialysis with the artificial kidney. The patient tolerated the first procedure well but died on the second day following the removal of the second adrenal, never having recovered consciousness. Postmortem examination revealed congenital aplasia of the left kidney, and a small kidney on the right which on microscopic section showed changes of chronic glomerular nephritis and pyelonephritis.

*Summary:* A 29 year old white male with long standing severe uremia, hypertension and retinopathy who died during the immediate postoperative period following the second adrenalectomy.

*Case 12 (K. MacC.).* This 41 year old white male accountant had been treated five months previously at this hospital for chronic glomerulonephritis with generalized edema and minimal azotemia. Various forms of therapy, including low-salt diet, intravenous albumin, administration of mercurial diuretics, a course of ACTH and application of Southey-Leach tubes had improved the edema only temporarily. The patient was re-admitted with extensive edema and found to have developed hypertension, believed to be based on his chronic glomerular nephritis. Physical examination showed enlargement of the heart to the left with normal rhythm; lung fields were clear. The liver edge was just below the costal margin and there was pitting edema of the lower extremities. The eye grounds showed recent hemorrhages bilaterally. The basal blood pressure ranged from 130/90 to 184/120 mm. of Hg. A seven foot heart film showed 22 per cent enlargement, and the vital capacity was 3,400 c.c. An electrocardiogram was normal. The serum cholesterol ranged from 435 to 1,210 mg. per cent. The urine contained 3 plus albumin, with the specific gravity fixed in the range of 1.005 to 1.016. The urine sediment contained five to 30 red blood cells per high power field and granular casts. Phenolsulfonphthalein excretion was 20 per cent in two hours. Blood urea nitrogen varied from 24 to 26 mg. per cent. The glomerular filtration rate was 20 c.c./min. Complete adrenalectomy was performed in one stage, and the postoperative convalescence was uncomplicated. Whereas the preoperative urinary sodium output ranged from 1.8 to 4.0 mEq. per day on a low salt intake, postoperatively urinary sodium excretion went as high as 124 mEq. on the same diet. During the months following surgery the patient lost 8 kg. of weight and was almost entirely free of edema fluid. Over the course of a year postoperatively the patient developed progressive renal failure and finally died in uremia.

*Summary:* A 41 year old white male who developed hypertension during the nephrotic stage of chronic glomerular nephritis. Complete adrenalectomy markedly improved the ability of the kidneys to excrete sodium, but blood pressure, cardiac status and retinopathy were unimproved.

*Case 13 (W. Co.).* The patient was a 29 year old white male who had had severe hypertension for five years. He had no history of congestive failure or renal insufficiency, but had been troubled for two years by severe throbbing headaches, marked fatigue and recurrent episodes of dizziness. His basal blood pressures ranged from 180/120 to 230/180 mm. of Hg. A seven foot heart film showed 20 to 25 per cent enlargement. His vital capacity was 3,700 to 4,500 c.c. His venous pressure was 135 mm. of saline. The arm-to-tongue circulation time was 23 seconds. During a sedation test the blood pressure fell from 200/130 to 160/100 mm. of Hg. Cardiac catheterization studies indicated early left ventricular failure. The urine contained 1 plus albumin, with red cells up to 10 per high power field. The blood urea nitrogen was 10 to 15 mg. per 100 c.c. Phenolsulfonphthalein excretion was 60 per cent in two hours, and the glomerular filtration rate was 128 to 136 c.c./min. (thiosulfate). The fundi showed marked AV nicking, with exudates on the right. An adrenalectomy was performed in two stages, the first complicated postoperatively by a transient right facial weakness. Postoperatively the basal blood pressure ranged between 130/90 to 150/100 mm. of Hg. Symptoms of dizziness and pounding headaches disappeared. Heart size was reduced to plus 6 per cent. Postoperatively the vital capacity was 4,100 c.c.; circulation time, 15 seconds; venous pressure, 110 mm. of saline. A renal biopsy showed fibrosis of occasional glomeruli with rare foci of interstitial fibrosis. Phenolsulfonphthalein excretion rose to 80 per cent, and blood urea nitrogen was 23 mg. per cent. The patient became able to do moderately heavy labor, being maintained on cortisone 25 mg. per day orally and 1 mg. desoxycorticosterone intramuscularly daily. On this program he did well until 11 months postoperatively, when he died suddenly as the result of an acute vascular accident. Postmortem studies revealed extensive coronary artery disease.

*Summary:* A severe hypertensive male with high-grade retinal changes, moderate cardiac involvement and minimal renal involvement, with a satisfactory response to bilateral adrenalectomy until sudden death intervened 11 months postoperatively.

*Case 14 (E. Gr.).* This 32 year old white male construction worker had a 10 year history of hypertension. During the two years prior to admission he had had ankle swelling, dizziness and weakness. The symptoms responded to a diet low in salt content. Two weeks prior to admission he developed episodes of paroxysmal nocturnal dyspnea, ankle edema and cough productive of blood-tinged sputum. He improved slightly following digitalization and administration of a rice diet. At the time of his admission his blood pressure was 220/140 mm. of Hg; there was a pulsus alternans, the heart was markedly enlarged by clinical examination, a seven foot film of the heart showed 27 per cent enlargement. There was a diastolic gallop rhythm at the apex. The fundi showed a papilledema, hemorrhages and exudates bilaterally. The urine contained 3 plus protein and hyaline and granular casts, and the specific gravity failed to rise above 1.014. His phenolsulfonphthalein excretion was 30 per cent in two hours. The electrocardiogram was characteristic of left ventricular hypertrophy. The patient's adrenals were removed in a one-stage procedure. Following the operation there was a rapid progression of renal failure, with the blood urea nitrogen rising rapidly to levels above 100 mg. per cent. He failed to show a sodium diuresis following adrenalectomy, and there was no postoperative lowering of the blood pressure. He developed a pericardial friction rub and the electrocardiogram showed evidence of potassium intoxication. He died suddenly one month following the removal of both adrenals. At postmortem examination there were nephrosclerosis

bilaterally, marked hypertrophy of both ventricles and acute fibrinopurulent pericarditis. Death was ascribed to aspiration of gastric content.

*Summary:* A 32 year old male construction worker with long-standing hypertension, retinopathy, cardiomegaly and moderate renal insufficiency. Following a one-stage bilateral adrenalectomy renal failure progressed, blood pressure was not lowered, and the patient died one month following operation.

*Case 15 (W. Mo.).* This 39 year old salesman was known to have had hypertension since the time of an insurance examination six years before his admission. During the year prior to entry he had had a retinal hemorrhage. He had been treated with a course of fever therapy and had been maintained on a diet low in salt, but his symptoms persisted. His initial examination revealed a blood pressure of 290/170 mm. of Hg. There was moderate papilledema in both retinæ, with narrowing and tortuosity of retinal arterioles. Scars of old retinal exudates were apparent. The lung fields were clear and the heart was slightly enlarged. An electrocardiogram was characteristic of left ventricular hypertrophy. Venous pressure was 40 mm. saline; circulation time, 20 seconds; vital capacity, 4,000 c.c. The urine contained 3 plus albumin, and the phenolsulfonphthalein excretion was 25 per cent in two hours. The blood urea nitrogen varied from 37 to 49 mg. per cent. He underwent a one-stage bilateral adrenalectomy. Following the operation he developed progressive azotemia, showed no improvement in his hypertension and failed to excrete increased amounts of sodium in the urine. Three weeks after surgery he developed several episodes of hyperkalemia with clinical signs of potassium intoxication. At the end of one month he developed pulmonary edema and tachycardia and died in shock. At postmortem examination he was found to have marked nephrosclerosis and coronary arteriosclerosis.

*Summary:* A 39 year old white salesman with hypertension of six years' duration, moderate retinopathy and moderate renal failure. He appeared to have no beneficial effects from bilateral complete adrenalectomy and died one month following operation.

#### ACKNOWLEDGMENTS

These studies were supported in part by grants from the National Institutes of Health of the United States Public Health Service, the Armour Laboratories and the Massachusetts Heart Association.

The authors are indebted to Dr. Harold F. Hailman, The Upjohn Company, Kalamazoo, Michigan, for Compound B used in these studies.

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## THE NATURAL HISTORY OF RHEUMATIC FEVER: A 20 YEAR PERSPECTIVE \*

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WE are presenting at this time a summary of the outstanding features of rheumatic fever, and its consequences in terms of heart disease and longevity. This report is in essence a review of 20 years' experience with this disease and of the facts and figures assembled from previous publications by the authors.† Our purpose is threefold: (1) to emphasize certain characteristics of the disease essential for its recognition; (2) to examine the validity and relative importance of these clinical features in the light of more than two decades of follow-up study, and (3) to assess those factors likely to be responsible for the amelioration in the incidence and severity of the disease apparent during the past 10 years. It is our hope that this perspective may serve as a suitable backdrop for the more recent and exciting trends in prevention and treatment, and in particular for the detailed studies to be reported by others on the program this morning. It may even serve as a basis of reference for future progress yet to be attained in this field.

The specific cause of the disease remains unknown. It has long been recognized as primarily a disease of childhood, and the onset reaches its peak in the decade between five and 15 years. However, no age group is immune, and initial attacks have been described in infancy and in old age. In the north temperate zone it is especially prevalent in the winter and spring months, and its victims are found most often in the needy population of our large cities, where overcrowding, undernutrition and unhygienic surroundings are apt to prevail. It presented to the Armed Forces a considerable problem in the training centers of World War II, as well as in the overseas theaters. It is unlikely that there exists a significant sexual, racial or physical predisposition to this disease, but the high family incidence is striking (Cheadle, 1889<sup>\*</sup>) with a recorded frequency of rheumatic heart disease varying between 39 per cent (St. Lawrence, 1922<sup>22</sup>) to 65 per cent (Wilson, 1940<sup>27</sup>). In fact, Wilson's studies have led her to the belief that hereditary susceptibility underlies the high familial incidence, and that predictions for sibling incidence in various matings can be made. It is also well known that rheumatic fever patients show a marked nonspecific hyperirritability to many stimuli. Although attacks are usually precipitated by streptococcal throat infections, they may also follow trauma, surgical operations, exposure to cold and even nonspecific protein shock reactions (Bland and Jones, 1935<sup>4</sup>).

\* From the Symposium on Rheumatic Fever presented at the Thirty-third Annual Session of the American College of Physicians, Cleveland, Ohio, April 25, 1952.

From the House of the Good Samaritan and the Massachusetts General Hospital.

† We are particularly grateful to Grune and Stratton and to Thomas Nelson & Sons for permission to use material and tables from previously published reports by the authors.

In this connection Waksman<sup>24</sup> (1949) has commented as follows: "What process is set in motion by these various events is not known; it may be the adaptation syndrome of Selye, a nonspecific allergic response, an increasing titer of autoantibodies against some constituent of connective tissue or even the reactivation of a latent virus infection."

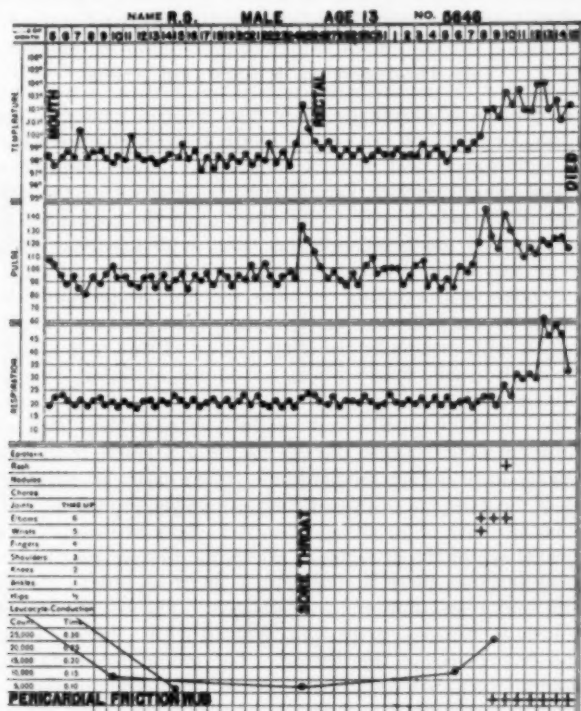


FIG. 1. Clinical chart showing the relationship between an upper respiratory infection and a subsequent recrudescence of fulminant rheumatic fever. (Bland and Jones, J. Clin. Investigation 14: 633, 1935.)

In any event, the dominant rôle of preceding streptococcal infection in the upper respiratory tract has been emphasized now for more than a quarter of a century (by Swift, by Zinsser and by others). This striking association is well shown by the clinical chart in figure 1, of a child 13 years of age recovering from previous rheumatic fever. Convalescence was interrupted by a sore throat and transient fever of 102° F. for 12 hours. This episode (so-called precipitating event) was followed by a latent interval (usually a few days to three weeks) before the onset of a severe and fulminating re-

crudescence of rheumatic fever and death. In carefully studied series this sequence is repeatedly observed, and studies at the House of the Good Samaritan, in Boston, indicate the presence of hemolytic streptococci during the throat infection in the majority (Jones and Mote, 1939<sup>15</sup>). These observations are in close agreement with subsequent studies elsewhere. With these facts in mind, we shall examine first those symptoms, signs and circumstances whereby rheumatic fever may be recognized.

### THE DIAGNOSIS OF RHEUMATIC FEVER

The recognition of rheumatic fever rests upon a number of symptoms and signs, no one of which can be considered entirely characteristic. Their diagnostic significance and relative importance have been reviewed by Jones.<sup>16</sup> The clinical pattern varies with the severity of the disease and with the age of the patient. In well defined cases the traditional symptoms are more evident at the onset, whereas later, with subacute activity, with recrudescence, and especially with severe and fatal recurrences, the symptomatology is often less orthodox. Under the last circumstance it is often confused with primary disease of the lungs (pneumonia) or the kidneys (nephritis), or with uncomplicated heart failure (Bland and Jones, 1938<sup>5</sup>).

The disease is usually ushered in by a cold or sore throat, as noted above. Poor health in childhood for which there is no obvious explanation is the usual picture. Loss of appetite and weight is often evident, and when daily temperatures are taken (preferably by rectum) a slight fever is the rule. Sicker patients have higher temperatures, often cyclic in character, and a quickening of the pulse out of proportion to the fever should excite suspicion. With this background of an ailing youngster, there are usually present one or more special symptoms or signs by which the disease may be recognized. For practical purposes there is considerable merit in Jones's classification<sup>16</sup> (1944) into major and minor manifestations. The so-called major manifestations include carditis, arthralgia and arthritis, chorea, subcutaneous nodules and recurrences of the disease. The minor manifestations include fever, abdominal pain, precordial pain, rashes, epistaxis, pulmonary changes (pleuritis and pneumonitis), and certain laboratory findings, nonspecific but helpful in arriving at a diagnosis.

*Carditis:* The most common and most serious and unequivocal manifestation of rheumatic fever is carditis. It is always found in fatal cases (Bland and Jones, 1938<sup>5</sup>), and its presence, associated with other evidence of rheumatic fever, can be assured with the appearance of significant murmurs, progressive cardiac enlargement, pericarditis (friction rub) or congestive heart failure under the age of 20.

The physical signs helpful in the recognition of early involvement of the heart are essentially those of mitral and aortic valve injury, usually associated with cardiac enlargement. These signs are often evident soon after the onset of rheumatic fever, and in some instances the appearance of

characteristic murmurs during an otherwise obscure illness directs attention for the first time to the rheumatic nature of the patient's poor health. Accuracy in diagnosis depends largely on proficiency in auscultation. In this connection the classification of murmurs on the basis of intensity (Levine, 1933<sup>17</sup>) has proved useful, as expressed in terms of gradation from very slight to very loud, as Grade 1 through Grade 5. In addition to intensity of the murmur, important clues are given by its character, location, transmission, relation to heart sounds, and to the effects upon it of respiration,

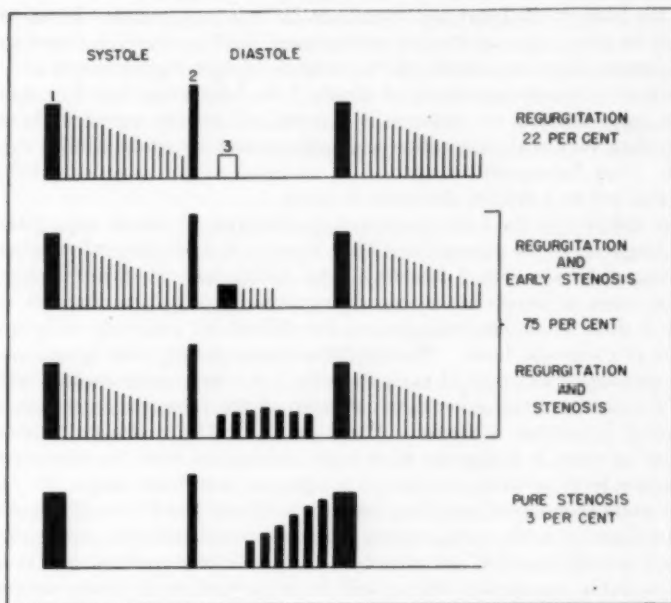


FIG. 2. Diagram of auscultatory signs of mitral valve involvement and their relative frequency in childhood. (Reproduced from "Rheumatic Heart Disease," E. F. Bland, Nelson's Loose-Leaf Medicine, 1951.)

exercise, and position of the patient. The quality and intensity of heart sounds, although important, are usually less informative than an accurate appraisal of murmurs. Thrills, if present, are helpful as confirmatory evidence, but they are often overemphasized, are occasionally confused with the shock of valve closure, and at times may actually be misleading.

*Signs of Mitral Valve Involvement:* A blowing systolic murmur maximal at the cardiac apex, of Grade 3 or greater intensity, is the most common auscultatory finding. It often tends to merge with the first heart sound, as is diagrammatically shown in the first section of figure 2. It is usually

well transmitted laterally to the left lung base. An associated systolic thrill is rare. This murmur, when it persists after active rheumatic fever has subsided, generally signifies mitral valve deformity with *regurgitation*. It is well to remember that lesser degrees of mitral regurgitation may be present temporarily, especially in children, as a result of mechanisms other than actual valve deformity. Transient murmurs of this degree may accompany cardiac dilatation during diseases other than rheumatic fever, especially when severe anemia is present.

Systolic murmurs of lesser intensity (Grades 1 and 2) at the apex and over the body of the heart are sometimes difficult to appraise. If unaccompanied by other signs of cardiac involvement, such as diastolic murmurs or enlargement, they are usually of "functional" (physiologic) origin and unimportant. Systolic murmurs of Grade 1 to 2 intensity heard to the left of the upper sternum are common in children and usually superficial in character; they vary with respiration and position and are of no clinical significance. Not infrequently a period of observation for several months is desirable before a definite diagnosis is made.

In addition to the loud apical systolic murmur of mitral regurgitation, a prolongation of the normal third heart sound into a minimal mitral diastolic murmur of Grade 1 to 2 intensity (also heard best at or just inside the cardiac apex, as shown in the second diagram of figure 2) is common, especially if there is cardiac enlargement (or dilatation) relatively early in the course of rheumatic fever. This additional auscultatory finding was at one time considered evidence of early stenosis, but more recent studies indicate that it is due to factors other than deformity of the valve, the most important of which is cardiac dilatation (Bland et al., 1935<sup>3</sup>). In a considerable number of cases it disappears after weeks or months with the subsidence of rheumatic fever, whereas in others it progresses to the next stage.

A more pronounced rumbling murmur of Grade 3 to 4 intensity in middle or late diastole at the cardiac apex, when associated with the previously described systolic murmur, indicates considerable deformity of the mitral cusps and probably actual stenosis as well as regurgitation in many instances, especially if accompanied by a diastolic thrill and a sharply accentuated first heart sound. However, here again dilatation of the heart, if considerable, may still be largely responsible for this diastolic rumble. It is evident from previous studies and from the foregoing remarks that an appraisal of the extent of mitral valve deformity in terms of anatomic stenosis is somewhat unreliable if active rheumatism and cardiac dilatation exist.

With the passage of years and the actual development of anatomic stenosis, there is a tendency for the apical systolic murmur (mitral regurgitation) to become less prominent, and for the diastolic murmur to acquire a coarser, rolling character, ending with a characteristic crescendo in a slapping first sound. A corresponding diastolic (presystolic) thrill and shock at the cardiac apex are usually palpable in well advanced cases. Accentuation of the pulmonary second sound indicative of mounting pressure

in the pulmonary circuit is the rule. In some instances no systolic murmur is audible, as indicated in the last diagram of figure 2, and "pure" or "adult" mitral stenosis is considered to be present. This so-called pure form (by auscultation) need not always represent a high degree of actual narrowing of the orifice, since relatively slight degrees of even this pure form are common. It is often accompanied by little or no cardiac enlargement and may be well borne for years without serious disability or apparent progression. Higher degrees, however, result in pulmonary hypertension, structural alterations in the lungs, and a characteristic syndrome of alarming (sometimes fatal) acute pulmonary edema and hemorrhage. This particular lesion requires a considerable time to develop (Bland et al., 1935<sup>8</sup>) and hence is infrequently encountered in childhood. More often than not it is the result of the mildest type of rheumatic fever (Walsh et al., 1940<sup>28</sup>) and frequently no clear history of such can be obtained. It is most often seen in females; and in those who give a positive rheumatic history, the incidence of childhood chorea is prominent.

*Signs of Aortic Valve Involvement:* Rheumatic involvement of the aortic cusps occurs in almost half the cases of rheumatic heart disease and is manifested by varying degrees of aortic regurgitation in the younger group. In the majority there is also disease of the mitral valve, but occasionally the aortic valve alone is involved. The physical signs of slight degrees of aortic regurgitation are often overlooked because of the prominence of coexisting signs of mitral valve disease in the same patient.

The characteristic murmur is diastolic and high-pitched (blowing) in character, appearing immediately after the second sound at the base of the heart, as indicated in figure 3. In the majority of cases, and if of only Grade 1 to 2 intensity, it is best heard to the left of the midsternal region in the second, third and fourth interspaces. It is important to remember that if the murmur is of slight intensity it may be heard only here near the sternal border, and usually best with the patient upright and at the end of expiration. Occasionally, and especially in children, it can be detected best with the patient recumbent, because of quieter heart action. If the degree of regurgitation is considerable and the murmur is loud, it is usually widely transmitted even beyond the cardiac apex. This wide transmission of aortic diastolic murmurs contrasts sharply with the localization of mitral diastolic murmurs of comparable intensity.

In the majority of instances of aortic regurgitation there is, in addition to the characteristic diastolic murmur, an accompanying basal systolic murmur of lesser degree, usually best heard (in contrast to the diastolic murmur) to the right of the upper sternum, the result of roughening and possibly stiffening of the leaflets. In the course of years, as in the evolution of mitral valve disease, the signs of regurgitation often become less pronounced, and are accompanied by increasing signs of stenosis, namely, an increase in the intensity and harshness of the systolic murmur, with the later appearance of a systolic thrill and a diminution or disappearance of the aortic second



sound. This gradual change requires many years before a high degree of stenosis becomes established, and is rarely encountered in childhood or even in early adulthood.

A perspective of the clinical patterns of rheumatic heart disease encountered in childhood and adolescence is well shown by a series of 709 patients under the age of 20 years (Bland and Jones, unpublished data) (figures 2 and 3). Auscultatory signs of mitral involvement were present in 695 (98 per cent). The remaining 14 patients (2 per cent) had aortic involvement without recognized signs of mitral disease. In those with

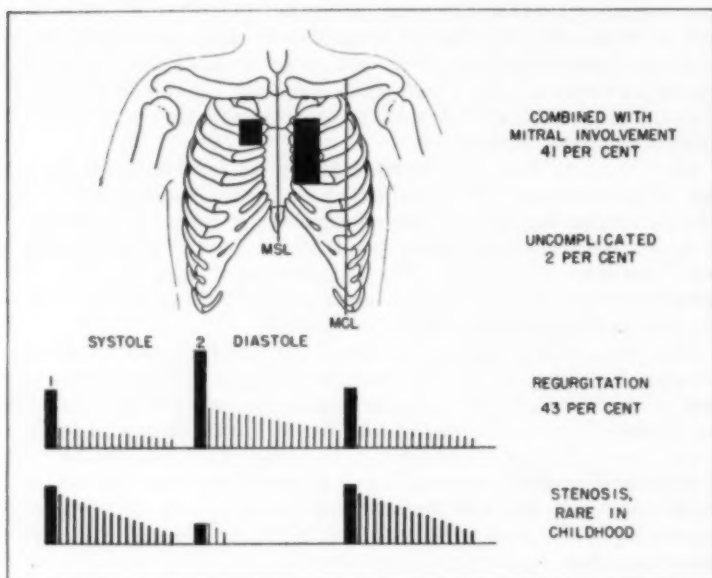


FIG. 3. Diagram of auscultatory signs of aortic valve involvement and their location and relative frequency in childhood. (Reproduced from "Rheumatic Heart Disease," E. F. Bland, Nelson's Loose-Leaf Medicine, 1951.)

mitral involvement, mitral regurgitation (apical systolic murmur) was present in 22 per cent; regurgitation and stenosis (the latter with the reservations previously noted) in 75 per cent; and "pure" mitral stenosis in 3 per cent. Of these 695 patients with mitral involvement, 290 (42 per cent) also had aortic regurgitation of varying degrees. It is to be noted that in comparing the physical signs in this clinical group with postmortem findings, there is close agreement in regard to mitral valve injury and a fair correlation in regard to aortic valve injury, but a notable absence in this youthful group of signs whereby tricuspid and pulmonary valve injury can be recog-



nized. Tricuspid involvement with advanced scarring in older patients can be suspected and often correctly diagnosed by the protection it affords the lungs in spite of heart failure, by prominent pulsations of the deep jugular veins and often of the liver, and occasionally by a suggestive murmur localized to the tricuspid area. However, it may be said that in childhood (and often in adults), rheumatic involvement of the tricuspid valve can rarely be recognized by auscultation because it is masked by the signs of coexisting mitral disease. To an even greater extent is the slight involvement of the pulmonary valve (occasionally found post mortem) obscured by the gross involvement of other valves.

In connection with the foregoing discussion of the auscultatory signs of rheumatic heart disease, it should be remembered that the degree of enlargement of the heart, broadly speaking, is the most reliable index of the extent of cardiac damage and of the future limitations of the patient (Grant, 1933<sup>14</sup>). An estimate of heart size by palpation and percussion can be attained with a high degree of accuracy in children with thin chest walls, and with considerable assurance in adults, but roentgen-ray examination (especially fluoroscopy) is more definitive and is invaluable in borderline cases.

*Arthralgia and Arthritis:* Pain is one of the most common presenting symptoms of rheumatic fever. The arms and legs are usually the sites of the discomfort, and especially the joints. The pains may be mild and in some cases are interpreted as "growing pains." Although severe discomfort with actual swelling and redness of the joints is not uncommon at the onset, it is more characteristic of rheumatic fever (migrating polyarthritis) in adults than in children. Pain elsewhere in the body—in the precordium and the abdomen—is common with more severe rheumatic fever. In the authors' series, arthritis was present in 41 per cent, arthralgia in 40 per cent, precordial pain in 24 per cent, and abdominal pain in 11 per cent.

*Chorea:* Next to arthritis and arthralgia, the most frequent manifestation is chorea. In approximately one half (51 per cent) of the above series chorea has appeared at some stage of the illness. It begins as an unusual form of nervousness or awkwardness and is often first noticed at school. It usually becomes more pronounced later as purposeless jerking movements of the arms, legs and face. It may even temporarily affect the speech. Occasionally chorea is the only manifestation of rheumatic fever ("pure" chorea), but in most instances it is accompanied by other signs of the disease. Of all the rheumatic stigmata it is the one most limited to childhood and is infrequently seen after adolescence, except as a rare complication of pregnancy. It has a high predilection for females, who often gain weight to an unusual extent following its subsidence. The possible significance of these features warrants further study.

*Nosebleeds* occur in almost a third (27 per cent) of the children with rheumatic fever. Their repeated occurrence during obscure ill health should arouse suspicion.

*Nodules*, another and rather curious manifestation of rheumatic fever, are largely limited to the early decades. These small structures, about the size of a pea and sometimes a trifle larger, are present in approximately 10 per cent of cases. They appear under the skin, on the tendon sheaths at the elbows, knees, ankles and fingers, and often over the occiput in those regions most exposed to trauma. They are nontender and ultimately disappear completely. Structures clinically and histologically identical with naturally occurring nodules have been induced artificially in children with active rheumatic fever (Massell et al., 1937<sup>18</sup>). Nodules are of some clinical significance, since their presence is usually associated with severe rheumatic fever; a protracted course can be expected, and the heart is almost always involved.

*Skin Rashes* of the erythema marginatum type, pale pink in hue and often evanescent in character, are occasionally seen with rheumatic fever (8 per cent). They are apt to occur with a smoldering protracted form of the disease.

*Pulmonary Manifestations*: During acute, and usually severe, rheumatic fever pleural pain and friction rubs occasionally appear, and in very ill children areas of pneumonitis and consolidation are sometimes found. These findings (especially consolidation) are apt to be spotty in distribution, at times transient (a day or two) in duration, and variable in location, and they are often unaccompanied by significant amounts of sputum. These areas of consolidation in the lungs (peculiar in their clinical behavior and in their histologic appearance), often combined with circulatory congestion, form the basis of that intangible entity, "rheumatic pneumonia."

*Laboratory Aids*: The laboratory procedures most useful (and these include electrocardiography and roentgenography) are a hemoglobin determination and a leukocyte count (the former is usually slightly depressed and the latter slightly to moderately elevated), and an erythrocyte sedimentation rate. The last is particularly helpful in following to quiescence a recognized attack, and in excluding possible rheumatic activity in older patients with established valvular deformity where the more readily recognized symptoms and signs of the disease are usually absent. Under these circumstances the appearance of ill defined poor health associated with a significant lessening of cardiac reserve should always excite suspicion of subclinical rheumatic activity. A sharp reduction in vital capacity has been stressed as an important clue by Wilson.<sup>27</sup> More recently, indirect evidence pointing to possible rheumatic activity by means of antistreptolysin titers on the blood serum has been studied—since rheumatic fever is so often preceded by streptococcal throat infection, the finding of a normal titer during a suspicious illness is somewhat against rheumatic fever, although it can exist with normal titers.

*Roentgenography*: Roentgen examination is always helpful in the study and management of patients with rheumatic heart disease. It is particularly valuable in questionable cases and in differential diagnosis but, like other

laboratory procedures, it may be misleading if considered apart from the physical findings, electrocardiogram and other diagnostic measures. Not all patients with rheumatic heart disease show enlargement, but careful study reveals alterations in contour in the majority.

In early cases, especially in childhood, an increase in the cardiac silhouette indicates myocardial injury. Progressive enlargement of the heart in this group means active carditis. Conversely, a diminution in size indicates a subsiding process.

The increase in heart size is generalized in character and when of considerable degree assumes a water-bottle shape, often resembling the dilatation of severe anemia and avitaminosis (beriberi) and indistinguishable from acute pericarditis with effusion. A differential diagnosis from the latter may be difficult in childhood, since with severe rheumatic fever and carditis there is often a concurrent pericarditis, although rarely an embarrassing effusion.

Valvular lesions in the early stages cannot be diagnosed by roentgen-ray, and even in more advanced cases the roentgen findings should always be correlated with the physical signs. Careful fluoroscopic study provides the best index of the relative stress on individual heart chambers and upon the pulmonary circulation.

*Electrocardiography:* Electrocardiograms often reveal evidence of cardiac involvement during rheumatic fever. They are particularly useful in establishing a diagnosis in early and in questionable cases, and in detecting rheumatic activity in patients with known valvular disease. In more advanced cases they also provide a clue to the relative strain on individual cardiac chambers, and an effective method of following drug therapy (digitalis and quinidine). It is important to remember, however, that the changes in the electrocardiogram are nonspecific and, as with other laboratory procedures, must be considered in conjunction with the clinical findings. Children may even succumb to severe rheumatic fever and widespread myocarditis with normal electrocardiographic findings.

The incidence of electrocardiographic abnormalities during rheumatic fever has been reported as from 20 to 100 per cent, varying with the observer, criteria of abnormality, age of patient, frequency of tracings and severity of disease. A small, carefully studied series with daily electrocardiograms disclosed significant abnormalities in 35 of 37 patients (95 per cent) (Cohn and Swift, 1924<sup>9</sup>). In another series of 63 patients studied with daily tracings during an average hospital stay of 44 days, abnormalities were recorded in 100 per cent (Master and Jaffe, 1932<sup>10</sup>). On the other hand, Wilson<sup>27</sup> has cited two series consisting of 54 hospital and 880 ambulatory patients, with an incidence of 33 and 22 per cent, respectively. In the first group weekly tracings were taken; in the ambulatory group only sporadic records were available. A recent Navy series of 700 cases of rheumatic fever revealed an incidence of 20 per cent (Sokolow, 1948<sup>28</sup>). The experience at the House of the Good Samaritan, based on 17,900 electrocardio-

grams since 1928 (mostly on children and adolescents), indicates an incidence of abnormalities much nearer 20 than 100 per cent (Craigie et al., 1950<sup>11</sup>). At the latter institution, records are taken on admission and monthly thereafter, except in special instances requiring more frequent recordings.

In general the electrocardiographic abnormalities are of three types: (1) delayed auriculoventricular conduction, (2) alterations in the QRS, T, and P waves, and (3) disturbances of rhythm.

*Delayed Conduction:* A delay in auriculoventricular conduction time (the P-R interval) has proved the most useful electrocardiographic sign of rheumatic activity. It occurred in about 20 per cent of the House of the Good Samaritan series, and in 40 per cent of the fatal cases. High degrees of heart block are rare in childhood and adolescence, and complete heart block is infrequent even in adults with advanced rheumatic heart disease.

In evaluating the P-R interval in children it is important to consider both rate and age (Ashman and Hull, 1937<sup>2</sup>). A P-R interval up to 0.20 second is usually considered normal for adults, but an interval of 0.17 second may be abnormal for a child with a fast heart rate. In following the P-R interval, serial electrocardiograms are particularly helpful. However, delayed conduction of minor degree (P-R 0.21 to 0.22 second) may persist for months and occasionally for a year or two after other signs of rheumatic activity have subsided. Under these circumstances it is impractical to consider it a sign of persistent activity if other evidence is lacking. Furthermore, in the presence of digitalis the effects of this drug in contributing to a prolonged conduction time must always be taken into account.

*Alterations in the QRS, T, and P Waves:* Significant delay in intraventricular conduction during rheumatic fever is rare (Filberbaum et al., 1946<sup>12</sup>). No instance of bundle branch block was encountered in the fatal cases studied by Bland and Jones,<sup>8</sup> although minor degrees of slurring and splintering of the QRS complexes were occasionally seen. In older patients with advanced valvular disease and hypertrophy, intraventricular block may be found, but even under these circumstances it is infrequent.

Right axis deviation is common in older patients with mitral stenosis of considerable degree and reflects strain and hypertrophy of the right ventricle. Conversely, disease of the aortic valve is apt to be associated with left ventricular strain and hypertrophy and left axis deviation in the electrocardiogram. With combined mitral and aortic valve disease the electrocardiographic patterns are often inconclusive and puzzling, combining the effects of strain and hypertrophy on both sides of the heart. An interesting shift in axis deviation to the right is sometimes seen in children with severe carditis, dilatation and congestive failure, with a subsequent return toward normal with recovery (Walsh and Sprague, 1941<sup>28</sup>) (figure 4).

Depression or elevation of the S-T intervals and inversion of the T waves during the course of rheumatic fever usually indicate pericarditis. At times

these changes in older patients may be confused with those of myocardial infarction; in the former, abnormal Q waves are absent, whereas in the latter they are almost the rule.

In 1937 attention was called to prolongation of the Q-T interval during rheumatic fever (Draue et al.<sup>12</sup>). More recently (1947) Taran and



FIG. 4. Serial roentgenograms and electrocardiograms from a child with severe rheumatic fever, cardiac dilatation, congestive failure and right axis deviation.

The progressive improvement is strikingly displayed by the decrease in heart size by roentgen-ray and a return to normal axis by electrocardiogram at the end of three and one-half months. (B. J. Walsh and H. B. Sprague, *Am. J. Dis. Child.* 61: 1003, 1941.)

Szilagy emphasized the importance of the Q-T interval as a more sensitive indicator of rheumatic activity than other electrocardiographic changes. However, subsequent studies by others (Pokress and Goldberger, 1949<sup>20</sup>; Craige et al., 1950<sup>11</sup>) suggest that, although they consider the Q-T deter-

mination a useful measurement, the necessity for careful correction in terms of age and heart rate limits somewhat its practical value.

Prominent broad and notched P waves suggest auricular hypertrophy and dilatation as a result of chronic mitral valve disease, particularly stenosis. They reflect long-standing structural changes and are of no value in appraising rheumatic activity.

*Recurrences of Rheumatic Fever:* Striking features of this disease are its chronicity and its tendency to recur. The degree of disability and the ultimate longevity of those with injured hearts are largely influenced by the frequency, duration and severity of recurrences. The last is by far the most significant factor. From the 20 year follow-up studies of Bland and Jones<sup>7</sup> (1951), an estimate of the incidence of these recurrences is shown in figure 5:

ATTACKS OF RHEUMATIC FEVER AND CHOREA BY YEARS

YEARS FROM ONSET	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
PATIENTS WITH R.F.	979	232	216	175	111	120	130	114	67	71	65	60	42	38	30	12	12	12	10	8
PERCENT OF LIVING	98	23	23	18	12	13	15	13	8	8	8	7	6	5	4	1.5	1.5	1.6	1.4	1.1

\* 21 patients had rheumatic heart disease without rheumatic fever when first seen.

FIG. 5.

they occurred in approximately one in five per year during the first five years, one in 10 during the next five years, one in 20 during the third five-year interval, and much less frequently in the final five-year period. It is important to remember that during the latter years of this tabulation the more susceptible individuals had succumbed and the survivors were well into early adult life. These figures are encouraging for the older age group. It is our belief from these studies that in terms of a young individual (under 20) there is a 60 to 70 per cent chance of recurrence during the first 10 years after the initial attack. This is in close agreement with the 68 per cent incidence noted by Roth, Lingg and Whittemore.<sup>21</sup>

In adults with rheumatic heart disease the appearance of poor health, sharply reduced reserve (and vital capacity), and otherwise unexplained elevation of the erythrocyte sedimentation rate should arouse suspicion of rheumatic activity. More overt signs are often lacking. Furthermore, in regard to chronicity, new evidence assembled during the past five years from



atrial biopsies at the time of mitral valve operations show Aschoff bodies in 20 to 25 per cent of cases. In view of the scant evidence under these circumstances of clinically detectable rheumatic activity and the absence of significant postoperative reactivation, there is need for a further critical review of these clinical pathologic relationships and perhaps some modification in our present concepts of "activity."

*Heart Failure in Childhood:* The occurrence of congestive failure in a child under the age of 20 with rheumatic heart disease is reliable evidence of active rheumatic infection, and even in older patients is highly suggestive of such. In the childhood group normal rhythm is the rule; in later decades auricular fibrillation is usually present (with mitral stenosis) and may contribute to, or precipitate, failure.

Circulatory failure in children is characterized by features seldom encountered in older patients (Walsh and Sprague, 1941<sup>26</sup>). It is primarily "right-sided" failure, with enlargement of the liver, puffiness of the face and unexpected weight gain in an ailing youngster (due to fluid retention). These signs appear as a rule in the order named above. Pulmonary râles are seldom heard until rather late in the illness. A high venous pressure is evident from the onset, and a remarkable shift in the electrical axis to the right is often recorded by the electrocardiogram, coinciding with the predominant dilatation of the right ventricle (figure 4). A loud gallop rhythm is the rule.

#### THE CONSEQUENCES OF RHEUMATIC FEVER

The first serious attempt to assess by long-term observation the outcome of rheumatic fever was begun before World War I by Cary Coombs in England and completed in 1922. Starting with an initial group of 253 children with cardiac involvement, he was able to trace 218 for the first year and 204 for five years, but only 177 for 10 years, with a mortality of 5.1, 11.2 and 21.4 per cent, respectively. Later studies by Ash in Philadelphia<sup>1</sup> (1948) and Wilson in New York<sup>28</sup> (1948) are notable and serve as a basis for comparison with our own experience in Boston. There has been a remarkably close agreement as to the outcome.

Our own studies in this connection are based upon 3,000 children and adolescents who have received protracted hospital care for rheumatic fever at the House of the Good Samaritan in Boston since 1921. A long-term program for follow-up was organized in 1928 and has been carried forward without interruption, with special emphasis on the original 1,000 patients who entered the series between 1921 and 1931. Twenty years have now elapsed on each of this latter group, and their course has been recently reported in detail elsewhere (Bland and Jones, 1951<sup>7</sup>). The following tables from this report summarize their original status and subsequent course:



TABLE I\*  
SUMMARY OF TWENTY YEARS OBSERVATION  
(1000 PATIENTS - 1921-51)

	PRHD	RHD	DEAD
ORIGINAL STATUS (average age = 8 years)	347	653	—
TEN YEARS LATER (average age = 18 years)	323	475	202
TWENTY YEARS LATER (average age = 28 years)	319 (3 lost)	380 (2 lost)	301

\* This and the subsequent tables are from Bland and Jones, *Circulation* 4: 836, 1951.

About one third (301) have died in the 20 year period, and of these more than one third (112) succumbed in the first five years of their disease. The cause of death in the 301 fatal cases is indicated as follows:

TABLE II

CAUSE OF DEATH (301 CASES) 20 YEAR DATA (TENTATIVE)		
RHD		
RHEUMATIC FEVER	}	231 (80%)
CONGESTIVE FAILURE		
SUBACUTE BACTERIAL ENDOCARDITIS - 26	}	30 (10%)
ACUTE BACTERIAL ENDOCARDITIS - 4		
OTHER CAUSES:		30
CEREBRAL EMBOLISM		3
SUDDEN & UNEXPECTED		10
UNCERTAIN		8
UNRELATED DISEASE OR ACCIDENT - 9		
PRHD		
UNRELATED DISEASE OR ACCIDENT		10

These data from the fatal cases support the experience of others as to the overwhelming rôle of rheumatic fever in the early decades. A further appraisal of its more serious manifestations in terms of prognosis is shown in table 3.

A greatly enlarged heart or congestive failure early in the disease exacted the highest toll, with an 80 per cent mortality in 20 years, mostly in the first decade. Pericarditis, subcutaneous nodules and acute arthritis occupied

intermediate positions, with 63 per cent, 37 per cent and 27 per cent mortality in the 20 year period. In contrast, chorea characteristically was associated with a benign form of the disease (12 per cent mortality). There exists, of course, much overlapping of this symptomatology.

Those who begin their rheumatic career with considerable cardiac enlargement do poorly, and it is unusual for patients who survive adolescence with greatly enlarged hearts to attain the age of 30. This is in accord with Grant's<sup>14</sup> observations in adults. On the other hand, little or no cardiac enlargement early in the disease speaks for a higher degree of natural resistance, relative freedom from serious recurrences, and a longer life.

The incidence of bacterial endocarditis parallels remarkably its incidence in other series. All the fatalities in our group antedated the penicillin era. Since then, six additional cases have been rescued with antibiotics, and none has been lost.

TABLE III  
PROGNOSIS  
(SOME SPECIAL FEATURES)

ONSET (NO. CASES)	10 YEARS (FATALITIES)	20 YEARS (FATALITIES)
	GREATLY ENLARGED HEART	
70	56 (80%)	57 (81%)
	CONGESTIVE FAILURE	
207	148 (71%)	152 (80%)
	PERICARDITIS	
130	73 (56%)	77 (63%)
	NODULES	
88	34 (38%)	37 (43%)
	ARTHRITIS	
410	91 (22%)	109 (27%)
	CHOREA	
518	49 (9.4%)	64 (12%)

Two decades of observation on this youthful group have provided an opportunity to study certain of the less well known features of rheumatic heart disease during the formative years. Of special interest have been the gradual disappearance of all signs of heart disease in a considerable number, and, in a comparable group, the insidious appearance of mitral stenosis after 15 to 20 years of good health without intervening signs of infection or heart disease (table 4). These two groups require further consideration.

*The Disappearance of Rheumatic Heart Disease:* At the onset of our observations there were 653 patients with signs of well defined rheumatic heart disease. At the end of 10 years the physical signs of valvular disease had disappeared in 76 (11 per cent) instances, and at the end of 20 years in 108 (16 per cent). In the majority this improvement consisted in the regression and ultimate disappearance of murmurs at the cardiac apex—a

diastolic rumble as well as a blowing systolic murmur of Grade 2 or greater intensity (classification of Levine)—and a return to normal where cardiac enlargement was originally present. In an occasional instance a blowing diastolic murmur (slight aortic regurgitation) of Grade 1 to 2 intensity has been observed to disappear. We suspect that minimal scarring persists in spite of the absence of murmurs or enlargement. Postmortem examination in one instance following accidental death supports this suspicion, as does the insidious appearance of mitral stenosis in a few patients 10 to 20 years later. In no instance have an aortic diastolic murmur of Grade 2 or greater intensity or the signs of established mitral stenosis disappeared.

*The Delayed Appearance of Rheumatic Heart Disease:* The counterpart of the above group is represented by those who recovered unscarred from their original rheumatic fever (347 cases), but who in later years, insidiously and often without further recognizable rheumatic activity, developed signs of valvular damage, most often "pure" mitral stenosis. The incidence of this variant is shown in table 4, where valvular disease was evident at the

TABLE IV  
DELAYED APPEARANCE OF RHEUMATIC HEART DISEASE

PRHD } 347	20 years later	{ RHD 154	2/3 without R F
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REGRESSION OF RHEUMATIC HEART DISEASE

RHD } 653	20 years later	{ PRHD 108 { less RHD 99
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end of 10 years in 83 (24 per cent), and at the end of 20 years in 154 (44 per cent). The span of our observations includes a number whose valvular deformity has not become evident for from 15 to 20 years later. Chorea has been a prominent feature of their original illness. The mechanism underlying this remote appearance of deformed valves is not clear. In only one third of this group was there clear evidence of recurring rheumatic activity. It may be that minimally scarred valves (initially silent as far as physical signs are concerned) provide a locus for the occasional but repeated deposition of platelet thrombi which in turn over the years become incorporated in the valve substance resulting in an ultimately deformed and stenotic orifice. This possible mechanism needs further study.

*The Subsequent Course of Mitral Regurgitation:* The ultimate status of those patients who originally had only a Grade 2 or greater systolic murmur at the cardiac apex is of some interest, especially in connection with the well known difficulties in properly assessing this physical sign. There were 87 patients in this category. Their subsequent course during the next two

decades is shown in table 5. In approximately one third the murmur disappeared, in another it remained unchanged, and in the final third there has been a slow progression of physical signs with the acquisition of a diastolic murmur at the apex. The course of this group has been most benign in terms of disability and death.

*The Development of Pure Mitral Stenosis:* The signs of so-called pure mitral stenosis—a late diastolic roll at the cardiac apex, ending with crescendo in a sharp first sound, unaccompanied by a systolic murmur—ultimately appear in a considerable number. They represent a gradual

TABLE V  
POST RHEUMATIC FEVER  
APICAL SYSTOLIC MURMURS  
(GRADE 2+)

87 CASES				
20 YEARS LATER				
PRHD	MR	MR+S	MS	
29 (33%)	35 (40%)	16 (19%)	7 (8%)	
Dead	5	4	•	10 %
(HGS 20 year series)				

evolution of the signs of mitral valve injury. The time element is variable in that some acquire a high degree of stenosis in five years, whereas others fail to do so in 50; the difference between the two usually is not apparent. This pattern of pure stenosis has evolved in 117 patients, but in only 12 has evidence of serious pulmonary hypertension appeared (acute pulmonary edema). The details are shown in table 6. In many of this group the first sign of valvular deformity was the delayed appearance of the diastolic murmur years after the original illness; in others, the typical signs slowly evolved from preëxisting signs of valve injury.

TABLE VI  
THE EVOLUTION OF MITRAL STENOSIS

ORIGINAL STATUS			
PRHD	MR	MR+S	MS
42	7	64	4
TEN YEARS LATER			
17	7	53	40 (5DIED)
TWENTY YEARS LATER			
117 (13DIED)			

ACUTE PULMONARY EDEMA • 12  
PRECIPITATED BY PREGNANCY • 3  
7 DIED, 5 LIVING

It is important to remember that even this pure form of mitral stenosis (by auscultation) need not always represent a high degree of actual narrowing of the orifice, and relatively slight degrees accompanied by little or no cardiac enlargement may be well borne for years without serious disability or apparent progression. Therefore, the suggestion recently advanced that early valvulotomy under these circumstances might prevent the later development of higher degrees of obstruction and thereby protect the lungs seems too drastic. It might actually promote the undesirable features it is designed to prevent, and hence for the present the considerable risk of surgery had best be reserved for those in actual need of relief.

*Aortic Valve Involvement:* Involvement of the aortic valve manifested by a characteristic blowing diastolic murmur was present initially in 194 patients and appeared subsequently in 179 others, so that during the 20 year period 373 patients showed signs of aortic regurgitation (58 per cent of the 653 with rheumatic heart disease). In 27 instances the aortic diastolic murmur was the only evidence of cardiac involvement; in the remainder there were coexisting signs of mitral valve disease. In nine instances the diastolic murmur of slight aortic regurgitation disappeared during later years. Severe angina pectoris decubitus occurred in six patients; each had a high degree of aortic regurgitation with a diastolic blood pressure approaching zero.

At the end of 20 years, 699 of the original 1,000 patients remain alive. Their average age is now 28, but a considerable number are in the fourth decade. The majority are remarkably well. Their limitations are as follows:

None-Slight	Moderate	Marked	Lost	PRHD *	RHD †
555	133	6	5	316	239

\* Potential rheumatic heart disease.

† Rheumatic heart disease.

It is encouraging that three out of four of the survivors have little or no limitation.

#### CONCLUDING REMARKS

In concluding this review of the manifestations and consequences of rheumatic fever it is appropriate to emphasize those measures which have contributed significantly to its control and which should continue to modify favorably the course of rheumatic heart disease. These are:

Preventive Programs	Sulfa compounds (1935)
	Antibiotics (1942)
Hormone Therapy	ACTH (1949)
	Cortisone (1942)
Prevention and Cure of Bacterial Endocarditis	Antibiotics (1942)
Surgery of the Heart	Valvulotomy (1923)
	Shunts (1948)
	Commissurotomy (1949)

Although the cause of rheumatic fever remains undetermined, its ultimate solution is inevitable. Evidence indicating a better control and lessening severity is fairly convincing. The long waiting lists of 10 years ago for available facilities no longer exist. The more severe manifestations of pericarditis, pleuritis, pneumonitis and childhood congestive failure are less often encountered. It seems unlikely that this represents merely a cyclic abatement of the disease. The final solution lies in the future, but until then the currently assembled facts justify an attitude of optimism and hope.

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## PRESENT STATUS OF DIAGNOSTIC TESTS FOR RHEUMATIC FEVER\*

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THE diagnosis of rheumatic fever offers no difficulties in those cases which present the classic clinical picture. Due to the great variability of the disease, however, only a minority of the total cases fall into this category, and it is frequently necessary to look to the laboratory for assistance in establishing the diagnosis. In view of this fact, it is unfortunate that none of the many tests employed provides an unequivocal answer concerning the occurrence of the disease. At the present time, no laboratory test is available which is comparable in its significance to the serologic tests for syphilis or to the specific bacteriologic and serologic procedures used in a variety of other infectious diseases. The various tests that have been recommended as aids in the diagnosis of rheumatic fever, since they lack specificity and are inconclusive by themselves, can be used only as a source of additional information to be considered along with clinical data in weighing the evidence for and against the diagnosis. It is important, therefore, to evaluate accurately the tests employed and to be aware of their limitations.

The laboratory procedures currently used in the diagnosis of rheumatic fever can be logically divided into two groups. The first group consists of tests for antibodies against certain of the products of group A streptococci. Since rheumatic fever is preceded by a streptococcal infection, the formation of antibody to streptococcal antigens is part of the over-all picture of the disease, and titrations of these antibodies may be regarded as semi-specific diagnostic procedures. However, it is obvious that the antibody tests cannot have absolute diagnostic specificity, since the majority of patients with streptococcal infections develop antibodies but only a small percentage have clinical rheumatic fever. The most that one can expect of these determinations is to provide evidence of a recent streptococcal infection, which, in the presence of clinical symptoms suggesting rheumatic fever, gives additional support to the diagnosis. In contrast to the antibody determinations, the tests of the second group are completely nonspecific and for the most part reflect changes that take place in the blood during the acute phase of many different disease processes. These nonspecific tests are typified by the most widely used of the group, the determination of the erythrocyte sedimentation rate. Some of the factors involved in the interpretation of the tests belonging to the two groups will be considered in the discussion which follows.

\* From the Symposium on Rheumatic Fever presented at the Thirty-third Annual Session of the American College of Physicians, Cleveland, Ohio, April 25, 1952.

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By far the most commonly employed of the antibody titrations is the measurement of antistreptolysin O, introduced by Todd in 1932.<sup>1</sup> This procedure has numerous advantages: it is relatively simple, gives precise and reproducible results when properly carried out, and measures an antibody which shows a significant increase in a high percentage of patients following streptococcal infection. More limited investigations have been made of the antibody response to a variety of other streptococcal antigens, such as streptokinase and streptococcal hyaluronidase, but the procedures used have for one reason or another proved less adaptable to general use. The pattern and significance of the antibody response are much the same in the case of each of the antigens, and consequently it will be sufficient to discuss the problem in terms of the most practical of the tests, the titration of antistreptolysin O.

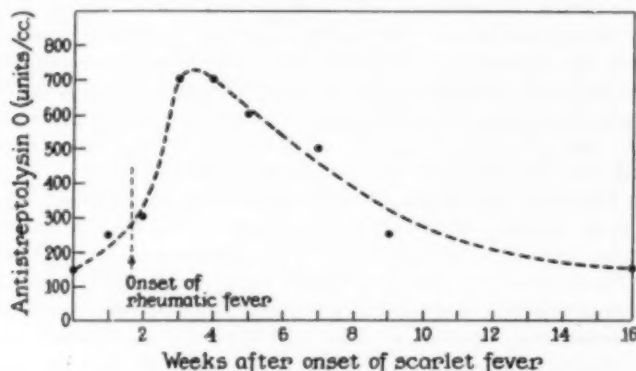


FIG. 1. Variations in antistreptolysin O titer in case of rheumatic fever following scarlet fever.

The general characteristics of the antistreptolysin O response in rheumatic fever are reflected by the data plotted in figure 1, which illustrates the variation of the antibody level in a single case occurring after an attack of scarlet fever. This is meant only to illustrate the most common pattern of response, but the particular case chosen also represents an approximation of the mean response of a large group of rheumatic fever cases. It must be realized that the quantitative variations from patient to patient are marked, and that some individuals show no change whatever in antistreptolysin O, while others have much higher titers than illustrated here. The main points to note are the rapid rise in antistreptolysin O during the first three to four weeks after the streptococcal infection, followed by a fall at a somewhat slower rate after the peak has been reached. It will be observed that the onset of rheumatic symptoms occurred while the curve was still rising. This

is the usual finding, and in the great majority of patients seen early in the course of rheumatic fever the titers of the various antistreptococcal antibodies have not yet reached maximal values.

From the point of view of diagnosis, one of the implications of the behavior of the antistreptolysin O titer, as illustrated in figure 1, is that the time at which serum is obtained for testing is of considerable importance. This is particularly true in chronic or polycyclic cases, in which evidence of disease activity can continue for months. The progressive fall in antistreptolysin O may occur in the face of continued rheumatic activity, and consequently a sample of serum drawn late in the course could give a value in the so-called normal range and thus be useless as a diagnostic aid. An

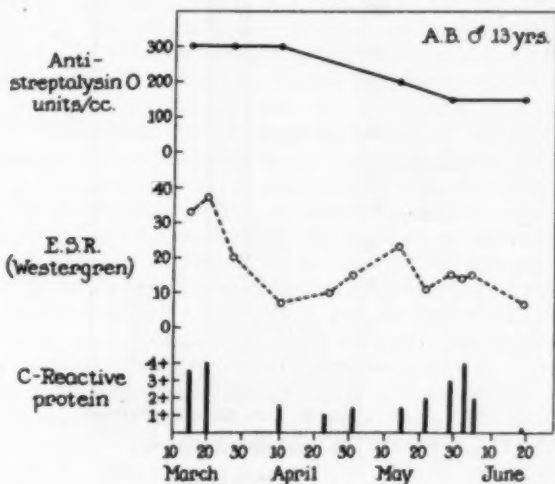


FIG. 2. Rheumatic activity in a chronic case with falling antistreptolysin O titer.

example of the progressively falling antibody titer in chronic rheumatic activity is presented in figure 2. This patient had shown unequivocal evidence of rheumatic fever for several months and the antistreptolysin O titer of the serum gradually declined. The segment of the clinical course illustrated in figure 2 covers the period during which the titer fell to a level that is considered in the normal range (150 units per cubic centimeter). Rheumatic activity during this period was manifested by fever, persistent carditis and recurrent subcutaneous nodules, as well as by an elevation of the sedimentation rate and the presence of C-reactive protein in the serum. While the diagnosis was never seriously in doubt in this particular case, the clinical picture in chronic rheumatic fever is frequently less well defined. In those protracted cases which present a diagnostic problem, the duration of disease

is of importance in evaluating the significance of an antistreptolysin O determination.

The distribution of the maximal antistreptolysin O titers observed in a series of 46 consecutive cases of early rheumatic fever at the Hospital of The Rockefeller Institute is presented in figure 3. The majority of the patients had levels between 250 and 1,000 units per cubic centimeter, and the geometric mean titer of the group was approximately 500 units per cubic centimeter. It is apparent that most of these patients had titers well above those encountered in normal individuals, but it must be emphasized that all of

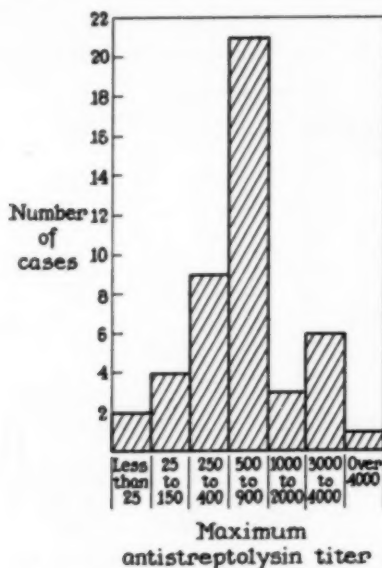


FIG. 3. Distribution of maximal antistreptolysin O titers in 46 consecutive cases of early rheumatic fever.

these patients were seen early in the course of the disease, so that the true maximal values were obtained in most instances. The two cases which showed maximal titers of less than 25 units per cubic centimeter are of interest, since both were children under five years of age. This is in accordance with the observation of others that very young children often show negligible antibody responses to the various extracellular antigens of the streptococcus following known streptococcal infections. The full significance of this observation is not clear, but it is another factor which must be considered in applying the streptolysin test to the diagnosis of rheumatic fever in young children.

When the antistreptolysin O titer is very high—e.g., over 1,000 units—as in 10 of the 46 cases included in figure 3, it is fairly safe to conclude that a recent streptococcal infection has occurred. On the other hand, a slightly or moderately elevated titer does not allow the same conclusion, and it is preferable not to rely on a single determination but to examine two or more successive serum samples in order to demonstrate whether a rise or fall in titer is occurring. As mentioned previously, a rising titer will ordinarily be encountered only for a short period after the first symptoms of rheumatic fever have appeared. However, in many cases the fall in titer after the maximal level is reached is sufficiently rapid to be demonstrated with sera obtained at an interval of one to three weeks and provide more adequate evidence of a recent streptococcal infection. Multiple determinations will thus occasionally clarify an otherwise equivocal result. For example, a titer of 200 units is a borderline result which is not very helpful, but if it represents a recent rise from a titer of less than 25 units it obviously reflects a significant antibody response. A relatively rapid fall from the level of 200 units to 100 units or below would strongly suggest a response of this type.

The usefulness of the antistreptolysin O determination in the differential diagnosis of rheumatic fever is well illustrated by two cases recently admitted to the Rockefeller Hospital on the same day. The first patient was a seven year old boy who was first seen in the fifth week of an illness characterized by fever and extensive involvement of the joints of the extremities and the spine. At the time of admission, hemolytic streptococci were not recovered from the upper respiratory tract, there was no unequivocal evidence of cardiac disease, and the nature of the widespread joint involvement suggested the possibility that the disease represented an early arthritis of the rheumatoid type rather than rheumatic fever. However, the antistreptolysin O titer was found to be 1,000 units, thus clearly indicating the occurrence of a recent streptococcal infection and supporting the diagnosis of rheumatic fever. The subsequent course of the disease confirmed this diagnosis.

A second patient was a 25 year old male who had also been ill for several weeks before admission. The chief complaints were persistent fever and weight loss, and the attending physician had noted a heart murmur which increased in intensity during the course of the disease. On admission the patient showed no evidence of joint disease, but a combination of fever, electrocardiographic evidence of a prolonged auriculoventricular conduction time, and a loud aortic diastolic murmur made it necessary to consider seriously the diagnosis of acute rheumatic fever. On the other hand, the history of a swinging type of fever, together with the occurrence of a few petechial lesions, brought up the possibility of subacute bacterial endocarditis. The antistreptolysin O titer was less than 25 units which, in an illness of this duration, was considered to be against the diagnosis of rheumatic fever. The diagnosis of bacterial endocarditis was shortly confirmed by the presence of viridans streptococci in successive blood cultures.

In summary, the measurement of antibodies against streptococcal antigens is employed to obtain information concerning the occurrence of recent streptococcal disease, and serves as a useful supplement to clinical data in the diagnosis of rheumatic fever when due consideration is given to the known characteristics of the antibody response. It should be pointed out that the significance of the antibody data does not appear to be affected by factors which might influence the specificity of the reactions. For example, there is no evidence for the occurrence of the hypothetical nonspecific anamnestic response of antistreptolysin O following non-streptococcal disease.

The laboratory tests of the second group, comprising the nonspecific procedures, are more accurately classified not as diagnostic tests but as indicators of rheumatic activity. Their major value comes in the evaluation of the degree of activity of the disease process once the diagnosis of rheumatic fever has been established. Each of the procedures included in this group is positive in a wide variety of diseases, some of which must be considered in the differential diagnosis of rheumatic fever. Despite the obvious limitations imposed by this fact, there are instances in which these tests can be employed to assist in the diagnosis of rheumatic fever. This is reflected in the generally accepted diagnostic criteria for rheumatic fever outlined by Jones in 1944.<sup>2</sup> Laboratory findings, such as those provided by the erythrocyte sedimentation rate and the leukocyte count, are included as one of the minor manifestations of the disease. This places these determinations in their proper perspective and relegates them to a secondary rôle. Thus, the minimal requirements for the diagnosis of rheumatic fever according to the Jones criteria are the presence of one major manifestation and at least two minor manifestations, and consequently the laboratory evidence is considered significant only in the presence of other clear-cut evidence of rheumatic fever.

The sedimentation rate has several shortcomings, even as a procedure for the estimation of activity of the rheumatic state, but its simplicity and lack of dependence on special reagents have given it a place as the best established test in this category. Different numerical results are obtained in the various technical modifications of the test, and accordingly absolute values for the normal and pathologic range cannot be given. However, the significance of the data provided by the sedimentation rate determination is essentially the same regardless of the technical procedure employed. The other commonly employed nonspecific test, the total leukocyte count, is less valuable because of the greater variation in the normal range and its relative insensitivity to alterations in rheumatic activity.

In addition to these standard procedures, a large number of other tests which reflect changes occurring in the blood during the acute phase of disease have been proposed for use in rheumatic fever. In general, the degree of specificity of these tests is not greater than that of the sedimentation rate. Several of these procedures are listed in table 1, illustrating the variety of

the acute phase reactions which can be used in this way. In most instances, these tests require considerably more elaborate technics than the determination of the sedimentation rate, and they have been employed in only a few clinics that have a special interest in their application.

In our laboratory the determination of C-reactive protein has been applied as a test for rheumatic activity, as well as a limited diagnostic tool in the same sense as the sedimentation rate. The results are sufficiently promising to make it regrettable that its general use is greatly limited by the difficulty of preparing the biologic reagents required for the method used in measuring this substance. The advantages of this test include the fact that C-reactive protein appears to be completely absent from normal blood, so that one does not have to deal with a troublesome normal range. Thus, the presence of even small amounts of this protein in the blood is indicative of an abnormal state, and the test has been useful when the sedimentation rate gives false or misleading evidence of rheumatic activity.

All of the nonspecific reactions may have their greatest value as diagnostic procedures when negative results are obtained. In other words, the tests

TABLE I

## Procedures Proposed for the Estimation of Rheumatic Activity

- Weltmann serum coagulation reaction.<sup>3</sup>
- Determination of serum mucoprotein.<sup>4</sup>
- Measurement of nonspecific hyaluronidase inhibitor of serum.<sup>5</sup>
- Measurement of C-reactive protein.<sup>6</sup>
- Bactericidal activity of blood vs. *Bacillus subtilis*.<sup>7</sup>
- Serum precipitation reaction with a quaternary ammonium salt.<sup>8</sup>

are so consistently positive in acute cases of rheumatic fever that the finding of a normal sedimentation rate or the absence of C-reactive protein in the blood of a patient suspected of having the disease is strong evidence against the diagnosis. There are certain exceptions to this rule, as in some cases of rheumatic fever with cardiac failure in which the sedimentation rate may be normal or inconclusive.

From this brief discussion, it is obvious that the nonspecific laboratory tests have only a limited usefulness in the diagnosis of rheumatic fever. Although not strictly relevant to the subject under discussion, it should be pointed out that they also have definite limitations in the detection of rheumatic activity. For example, all of these tests revert to normal when the symptoms and signs of rheumatic fever are suppressed by therapy with salicylates, cortisone or corticotrophin, even though the underlying disease process remains, as indicated by the rapid return of symptoms on withdrawal of the medication. Thus, the laboratory is of little assistance in guiding the duration of therapy required.

The present discussion has been limited to the purely laboratory aspects of diagnostic aids, thus omitting consideration of other procedures, such as electrocardiography. It is generally admitted that no single electrocardiographic abnormality is pathognomonic of rheumatic fever and none of them



occurs regularly in all cases, so that here again the findings can only supply additional evidence to be weighed in the course of differential diagnosis.

A critical evaluation of the diagnostic tests for rheumatic fever leads to the conclusion that none of those available at the present time is entirely satisfactory. The obvious need is for a single, specific test which will give an unequivocal answer to the question, Does this patient have rheumatic fever? Unless some reaction of this sort is encountered by accident, it is probable that we will have to await the development of a better understanding of the pathogenesis of the disease before a specific test will become available.

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## RECENT DEVELOPMENTS IN THE PREVENTION OF RHEUMATIC FEVER\*

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DURING the past decade developments in the control and prevention of rheumatic fever have occurred which, when fully applied, should reduce the incidence of a disease that is a major cause of death in children and an important cause of chronic disability in both children and adults.

It is now well established that attacks of rheumatic fever are usually, if not always, initiated by a preceding group A streptococcal respiratory infection. Recently developed technics which have been successful in lowering the incidence of rheumatic fever have been directed toward this streptococcal infection. Two methods utilizing these technics are now available for preventing rheumatic fever. One is the prevention of streptococcal infections by means of prophylaxis with sulfonamides or penicillin; the other is the treatment of streptococcal respiratory infections with penicillin or aureomycin.

In general, there are two population groups in which the problem of prevention of rheumatic fever must be considered. The first group consists of the general population which has not experienced an initial attack of rheumatic fever; the second group is comprised of those individuals who have experienced one or more attacks of the disease. The approach to the prevention of rheumatic fever is different in these two groups.

### PREVENTION OF THE INITIAL ATTACK OF RHEUMATIC FEVER

Prevention of the initial attack of rheumatic fever by means of chemoprophylaxis of streptococcal respiratory infections is not, as a rule, practical in the general population. The attack rate for rheumatic fever is relatively low in this group<sup>1</sup>; and the task of administration of prophylactic agents would be enormous. In certain closed population groups—for example, military establishments—during periods of time when streptococcal infections are epidemic, sulfadiazine prophylaxis is of value in reducing the expected incidence of rheumatic fever.<sup>2</sup> The use of sulfadiazine over a period of only a few months may not result in the development or spread of sulfon-

\*From the Symposium on Rheumatic Fever presented at the Thirty-third Annual Session of the American College of Physicians, Cleveland, Ohio, April 25, 1952.

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This investigation was conducted under the sponsorship of the Commission on Acute Respiratory Diseases and the Commission on Streptococcal Diseases, Armed Forces Epidemiological Board, and was supported by the Offices of The Surgeons General, Departments of the Army and Air Force, Washington, D. C.

amide-resistant strains of streptococci.<sup>2</sup> If strains resistant to the sulfonamides should be encountered, penicillin could be substituted as the prophylactic agent. Experience with penicillin used as a prophylactic agent against streptococcal infections occurring in large population groups is limited, and an adequate regimen for administering penicillin for the purpose of prophylaxis is not now available.

The second method for reducing the incidence of initial attacks of rheumatic fever is the treatment of the preceding streptococcal respiratory infection. Investigations<sup>3,4</sup> prior to 1949 had indicated that penicillin treatment of acute streptococcal pharyngitis reduced the incidence of rheumatic fever following this infection. Since 1949 extensive studies\* have been

TABLE I  
Effect of Penicillin or Aureomycin Therapy of Group A Streptococcal Pharyngitis on the Incidence of Initial Rheumatic Attacks

Treatment	Infections	Rheumatic Fever		
		Number	Per Cent	Per Cent Reduction
Penicillin treated control	1120	2	0.18	91.0
	1142	23*	2.01	
Aureomycin treated control	689	3†	0.44	81.4
	719	17	2.36	

\* Two of these patients at the time of admission for rheumatic fever gave a past history of rheumatic fever.

† One patient in this group also gave a history of rheumatic fever at the time of his rheumatic fever admission.

Aureomycin was supplied through the courtesy of Dr. Gladys L. Hobby, Charles Pfizer & Co. Inc., Brooklyn, New York.

conducted at F. E. Warren Air Force Base to determine the effect of treatment of streptococcal sore throat with either penicillin or aureomycin on the incidence of rheumatic fever. Table I summarizes the results obtained from that portion of the studies which has been completed.

The patients represented by the data appearing in this table had acute respiratory infections observed in the hospital by members of the staff † of the Streptococcal Disease Laboratory. The streptococcal etiology of these infections is indicated by the presence of tonsillar or pharyngeal exudate in all patients, by the recovery of group A streptococci from the admission throat culture of all patients, and by the presence of a white blood count of 12,000 or greater in 75 per cent of the patients. In addition, a significant

\* These studies have been reported in part.<sup>5,6,7,8</sup>

† Members of the staff of the Streptococcal Disease Laboratory during the period of these studies were, in addition to the authors, Dr. Charles H. Rammelkamp, Jr., Director, Major Floyd W. Denny and Captain Lewis W. Wannamaker, Assistant Directors, Major Edward O. Hahn, Captain William R. Brink, Captain Daniel Stowens, and Dr. Edward A. Custer.

increase in antibody (antistreptolysin "O") to the streptococcus was demonstrated in the convalescent sera of 82 per cent of the control patients. At the time of admission for their respiratory illness, all patients gave a history denying previous attacks of rheumatic fever. As is noted in the footnote to table 1, however, an inaccurate history was obtained from a few patients. All patients were seen at a follow-up examination three to five weeks following their respiratory illness.

The dosage of penicillin varied from a single injection of 600,000 units of procaine penicillin G in peanut or sesame oil containing 2 per cent aluminum monostearate, to four daily injections of 600,000 units of aqueous procaine penicillin with an injection of penicillin in oil on the fifth day. A majority of the patients received treatment which resulted in continuous concentrations in the body for at least five days. Aureomycin hydrochloride dosage varied from a total dose of 8.0 gm. in four days to 11.5 gm. in six days. The majority of the patients were treated for five days. The control patients in both groups, as a rule, received no placebo therapy, although a small number did receive such treatment.

Table 1 shows the effect of these two drugs on the incidence of rheumatic fever occurring less than 35 days after an observed streptococcal infection. Experience has shown that patients developing rheumatic fever longer than 35 days after a streptococcal infection almost invariably show bacteriologic, serologic or historical evidence of a second streptococcal infection.<sup>9</sup> Both penicillin and aureomycin were effective in reducing the incidence of rheumatic fever. The reduction in the attack rate for rheumatic fever in those patients receiving penicillin when compared to a similar group not receiving penicillin was 91 per cent. This compares to an 81.4 per cent reduction when aureomycin was used.

Studies which will be published in detail later indicate that persistence of the carrier state following treatment results in an antibody response of the same order of magnitude as in the untreated patients.<sup>8</sup> Since the attack rate of rheumatic fever in any population with acute streptococcal infections may be correlated with the magnitude of the antibody response,<sup>10</sup> it would appear that the ideal form of preventive therapy would be that which inhibited antibody production to the maximal degree. In these studies penicillin was more effective than aureomycin in reducing the streptococcal carrier state and in inhibition of antibody formation.<sup>8</sup> Thus it is to be expected that penicillin will also be more effective than aureomycin in reducing the incidence of rheumatic fever.

#### PREVENTION OF RECURRENT ATTACKS OF RHEUMATIC FEVER

Individuals who have had one or more attacks of rheumatic fever are especially likely to develop a recurrent episode of rheumatic fever following a streptococcal respiratory infection. Over a 20 year period at the House of the Good Samaritan in Boston, Massell<sup>11</sup> reports that among rheumatic

TABLE II  
Effect of Sulfonamide Prophylaxis on Rheumatic Fever Recurrences\*

Treated Group			Untreated Group		
Patient-Seasons	Recurrences		Patient-Seasons	Recurrences	
	Number	Per Cent		Number	Per Cent
1447	27	1.9	1739	241	13.9

\* The summary of Dodge<sup>14</sup> and the investigations of Baldwin,<sup>15</sup> Rubbo<sup>16</sup> and Feldt<sup>17</sup> are included in these data.

patients approximately 50 per cent have a recrudescence of rheumatic fever following a streptococcal infection. Thus the importance of controlling streptococcal infection in patients with a history of rheumatic fever is evident.

Since the reports of Coburn and Moore<sup>12</sup> and Thomas and France<sup>13</sup> in 1939 indicated that the daily administration of sulfanilamide to rheumatic subjects prevented streptococcal infections and recurrent attacks of rheumatic fever, many studies of the effect of sulfonamide prophylaxis have been recorded (table 2). Sulfanilamide or sulfadiazine administered in dosages varying from 0.5 to 3.0 gm. daily resulted in an 86 per cent reduction in recurrent attacks of rheumatic fever. At the present time, sulfadiazine in a dose of 0.5 to 1.0 gm. daily is usually employed.

More recently oral penicillin has been used as a prophylactic agent. Reported investigations are summarized in table 3. The variations in the manner of administration and form of oral penicillin, plus the small number of patients studied, do not permit a definitive interpretation of the results or a comparison of these results with those obtained with the use of sulfon-

TABLE III  
Effect of Oral Penicillin Prophylaxis on Rheumatic Fever Recurrences

Author	Therapy	Treated Group		Untreated Group	
		Patient Seasons	Recurrences	Patient Seasons	Recurrences
Maliner <sup>18</sup>	5000 unit troches 3 times a day continuously.	33	0	30	2
Kohn, Milzer and MacLean <sup>19</sup>	Two 100,000 unit tablets 4 times a day for 7 days at monthly intervals.	48	0	45	5
Evans <sup>20</sup>	1 daily dose 100,000 units calcium penicillin in $\frac{1}{2}$ oz. 5% glucose continuously.	155*	0	145*	4
	Total	236	0	220	11

\* Approximate.

amides. Since penicillin is effective in eradicating the streptococcus from carriers,<sup>21</sup> one would expect that it would be very effective in the prevention of streptococcal infections. Additional investigation is necessary, however, to determine the dosage and schedule of administration of penicillin which will be most effective. Penicillin may eventually become the drug of choice in prophylaxis against streptococcal infections, since it has been demonstrated that sulfadiazine prophylaxis does not prevent all recurrences of rheumatic fever.

In the absence of a completely satisfactory regimen for preventing streptococcal tonsillitis or pharyngitis, it is of great importance to recognize the occurrence of these infections in patients with a history of rheumatic fever. The data summarized in table 4 demonstrate that prompt and adequate penicillin treatment of such infections in rheumatic subjects decreases the recurrence rate of rheumatic fever. Each series of cases shows a marked reduction in number of recurrences of rheumatic fever in those patients who re-

TABLE IV  
Effect of Penicillin Therapy of Group A Streptococcal Pharyngitis on the Incidence of Recurrent Rheumatic Attacks

	Treated Patients			Untreated Patients		
	Infections	Recurrences		Infections	Recurrences	
		Number	Per Cent		Number	Per Cent
Massell et al. <sup>22</sup>	25	2	8.0	11	6	54.0
Streptococcal Disease Lab.	22	0	0	20	4	20.0
Total	47	2	4.3	31	10	32.3

ceived penicillin. Both of the patients in the treated group showing rheumatic recurrences also showed evidence of persistence of their infecting organism after cessation of treatment, and would therefore be considered as having received inadequate therapy. As was pointed out previously, eradication of the infecting organism may be necessary to prevent rheumatic fever.

The attack rate for rheumatic fever is lower in the patients studied at the Streptococcal Disease Laboratory than in those reported by Massell. The fact that the last episode of rheumatic fever in the former group of patients usually occurred several years before their observed streptococcal infection may explain this lower attack rate, since it has been demonstrated that, as the interval following an episode of rheumatic fever increases, the chance of a recurrent attack decreases.<sup>23</sup> The 20 per cent attack rate for rheumatic fever in this group is still considerably higher than the approximately 2.5 per cent rate for initial attacks of rheumatic fever, as shown in table 1. This

demonstrates the increased susceptibility that exists in rheumatic individuals when they acquire a streptococcal respiratory infection.

#### COMMENT

There is now considerable evidence which indicates that the incidence of both recurrent and initial attacks of rheumatic fever may be substantially lowered by the appropriate use of chemotherapeutic or antibiotic agents. Table 5 summarizes the procedures, based on our present knowledge, which are recommended in the management of rheumatic subjects and of non-rheumatic subjects who acquire a streptococcal respiratory infection.

Since approximately 40 per cent of streptococcal respiratory infections are either asymptomatic or so mild that medical care is not sought,<sup>9</sup> prophylaxis against such infections rather than dependency upon treatment of these infections once they occur is the method of choice in prevention of recurrent episodes of rheumatic fever. Patients who have active rheumatic fever or

TABLE V  
Recommendations for Prevention of Rheumatic Fever

Rheumatic Fever Experience	Prophylaxis	Treatment of Streptococcal Sore Throat
Recent attack	Sulfadiazine or penicillin administered continuously at least 3 years	Penicillin Immediate therapy for a minimum period of 10 days.
Remote attack or rheumatic heart disease	Variable	Penicillin Immediate therapy for a minimum period of 10 days.
None	None	Penicillin therapy for at least 6 days Aureomycin therapy for at least 7 days

who have recently had an episode of rheumatic fever should be placed on sulfadiazine prophylaxis since, at the present time, the regimen for penicillin prophylaxis has not been adequately established. Sulfadiazine should be given daily in a dose of 0.5 to 1.0 gm. for a minimal period of three years. In many instances it should be continued for longer periods of time, if exposure to streptococci is great or if a new attack of rheumatic fever would be of great risk to the patient. If a streptococcal sore throat occurs, prompt treatment with penicillin should be initiated and continued for a minimal period of 10 days. A desirable regimen would be 600,000 units of procaine penicillin G each day for the 10 days. Aureomycin should be reserved for only those patients who cannot tolerate penicillin, and when it is used a careful search should be made for evidence of clinical or bacteriologic relapse following therapy. Since eradication of the infecting organism is of great importance in preventing recurrences of rheumatic fever, it would be well also to follow penicillin treated patients with cultural studies to determine



if eradication of the organism has occurred. If the organisms have not been eradicated, prompt retreatment should be instituted.

In those patients whose last episode of rheumatic fever occurred more than two years previously, or in those patients with a history which is negative for rheumatic fever but who have evidence of rheumatic heart disease, the indications for prophylaxis are not so clearly defined. In general, if there is an undue risk of streptococcal infection, these patients should be protected with prophylaxis. In children of school age this risk usually exists during the school year and, more especially, during late winter and early spring. In adults, protection should be afforded during periods when streptococcal disease is epidemic. Therapy of acute streptococcal pharyngitis or tonsillitis when it occurs in these patients should be the same as in those patients with a recent attack of rheumatic fever.

Patients who give no history of rheumatic fever and who develop a streptococcal sore throat may be treated with either penicillin or aureomycin. Each of these drugs has certain disadvantages. Until an adequate dosage regimen for oral penicillin is established, penicillin should be administered by injection. To insure adequate treatment, return visits for the patient are necessary and these may be difficult to accomplish. Aureomycin has the advantage of oral administration, but the disadvantages of expense and dependence on the patient for administering his own therapy. The latter is especially disadvantageous, since many patients tend to stop taking a drug when they feel well, and, in addition, the gastrointestinal symptoms which frequently appear in association with aureomycin therapy will often result in premature discontinuance of the drug. Thus inadequate therapy may result when aureomycin is self administered. The greatest advantage which penicillin possesses over aureomycin is its ability to eradicate streptococci from the throats of a large proportion of patients with streptococcal respiratory infections. This advantage would make penicillin the treatment of choice. Effective penicillin blood levels should be maintained for at least six days, and aureomycin should be administered for at least seven days. That penicillin treatment may not prevent rheumatic carditis but may only suppress clinical manifestations of rheumatic fever has been suggested by Weinstein.<sup>24</sup> Preliminary studies by Hahn et al.<sup>6</sup> indicate that not all post-streptococcal electrocardiographic abnormalities are eliminated by either penicillin or aureomycin treatment. Until more definite results are available, however, it should be assumed that rheumatic carditis is prevented by adequate treatment of streptococcal sore throat with penicillin or aureomycin.

Streptococcal respiratory infections can be recognized in many instances. The onset is sudden, with soreness of the throat *on swallowing*, chills, feverishness and other constitutional symptoms, such as headache, myalgia and vomiting. On physical examination, tonsillar or pharyngeal exudate is observed in a large number of patients, and there are diffuse redness and edema of the pharynx and uvula. The lymph nodes at the angles of the jaw are enlarged and tender. A blood count will usually show a leukocytosis.

In most instances, a culture obtained from the throat will show a predominant growth of beta hemolytic streptococci. When facilities for bacteriologic diagnosis are not available, the symptoms and signs are sufficient both to establish a presumptive diagnosis of streptococcal pharyngitis and to indicate institution of treatment. In rheumatic subjects, initiation of therapy should not wait until the results of a throat culture are obtained.

#### SUMMARY

There are methods now available which, if utilized properly, should greatly reduce the incidence of both initial and recurrent attacks of rheumatic fever. These methods are directed toward the streptococcal respiratory infection that initiates an attack of rheumatic fever. Two methods which have been successful in lowering the incidence of rheumatic fever are, (1) prevention by chemoprophylaxis of the preceding streptococcal respiratory infection, and (2) treatment of this infection with penicillin or aureomycin.

In individuals who have had recent attacks of rheumatic fever and, in certain circumstances, individuals with less recent histories of rheumatic fever, prophylaxis of streptococcal infections with sulfadiazine is the method of choice for prevention of recurrences of rheumatic fever. When a streptococcal infection occurs in such individuals, treatment with penicillin should be started immediately and continued over a period of at least 10 days.

Individuals who have no previous history of rheumatic fever should receive either penicillin or aureomycin when they acquire a streptococcal respiratory infection. Penicillin possesses certain advantages over aureomycin and is the drug of choice. Prophylaxis against streptococcal infection is, as a rule, not practical in these individuals.

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## CASE REPORTS

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### THE ASSOCIATION OF MILIARY TUBERCULOSIS OF THE BONE MARROW AND PANCYTOPENIA \*

By THEODORE S. EVANS, M.D., F.A.C.P., VINCENT A. DELUCA, Jr., and  
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A PATIENT with pancytopenia recently came to necropsy in this hospital. A totally unsuspected disseminated tuberculous process was found in the viscera and bone marrow. It has been thought of interest to call attention to the alterations of the peripheral blood and bone marrow associated with miliary or disseminated tuberculosis, and to describe the findings in the present case.

#### LITERATURE

Alterations in the peripheral blood in tuberculosis were recognized in the earliest days of blood counting. Apparently the first report associating such changes with tuberculosis of the bone marrow is that of Donhauser<sup>1</sup> in 1908. In his patient, the bone marrow was markedly hyperplastic and many tubercles were present. In 1922 Wiechmann<sup>2</sup> observed numerous miliary tubercles of the bone marrow in two patients who had died of tuberculosis. The peripheral blood of these patients had shown a leukemoid reaction. Dyke<sup>3</sup> in 1924 first called attention to aplastic anemia in association with tuberculosis. His case number 4 appears to have been one of widespread miliary tuberculosis, proved at autopsy. In the bone marrow were many caseous tubercles in which bacilli were demonstrated. During life the peripheral blood picture was consistent with that of myeloid leukemia.

Following these early observations, a most significant contribution was made by Doan and Sabin.<sup>4</sup> In 1927 these investigators carried out classic experiments on the effect of experimentally induced tuberculosis on the blood and bone marrow of animals. In the first instance they called attention to the intimate relationship between tuberculosis and changes in the peripheral blood. Eighty rabbits were inoculated with a bovine strain of tubercle bacilli. All of the animals developed miliary tuberculous lesions of the bone marrow. Beginning on the eighth or tenth day large numbers of young monocytes were formed in the marrow. From the twelfth to the twentieth days typical epithelioid cells and giant cells of the Langhans type appeared. This new tuberculous connective tissue eliminated much of the fat of the marrow and encroached upon the blood-forming foci. The marrow tended toward spontaneous healing, provided the animals survived the first acute reaction sufficiently long. During and after the third month there was hyperplasia of the blood-forming elements in the bone

\* Received for publication September 15, 1951.

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marrow. Eventually the marrow became entirely normal in spite of steadily progressing, frequently fatal tuberculosis elsewhere in the body.

Early in the course of the experimental disease the peripheral blood showed a sharp fall in platelet count, anemia and a fall in the number of granulocytic white blood cells. These changes were correlated with the progressive involvement of the marrow by the tuberculous process. The onset of recovery was initiated by the return of the platelets to normal, by a rise in hemoglobin followed quickly by a rise in red cells, and by a more gradual increase in the granulocytes. Of especial interest was the definite increase in monocytes in the peripheral blood, associated with a corresponding fall in the lymphocyte count. As is well known,

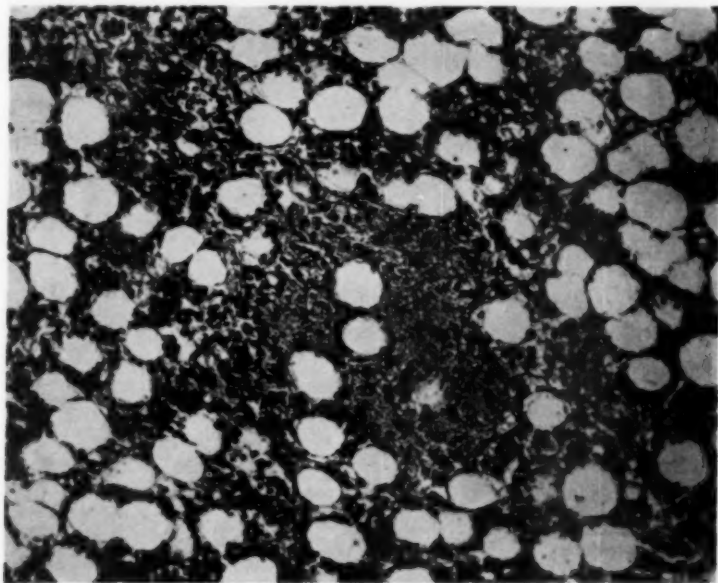


FIG. 1. Bone marrow.  $\times 120$ . Miliary tubercle.

this observation has been of clinical aid in following the progression or healing of the disease in man. Sabin and her co-workers further correlated the fall in the platelet count with the disappearance of megakaryocytes from the marrow. This observation subsequently led to the demonstration that the blood platelets are derived from the megakaryocytes.

In 1931 Doan and Moore<sup>6</sup> reported two patients with anemia and leukopenia. At necropsy widespread miliary tuberculosis was found, including involvement of the bone marrow. Custer and Crocker in 1932<sup>6</sup> described two patients with blood pictures of myelogenous leukemia who had associated tuberculosis. At postmortem, the bone marrow of the first patient was hypocellular, with myeloblasts and myelocytes predominating. Tubercles were found in the viscera but

no leukemic infiltration was present. In the second case the marrow was hyperplastic. Tubercles were widespread throughout the body, but there was no evidence of leukemia except for myeloid metaplasia in the spleen. Kriech and Heni<sup>7</sup> in 1935 examined the bone marrow of a patient with miliary tuberculosis. The peripheral blood had shown a severe pancytopenia. They describe aplasia of the red cell elements of the marrow. Fortunato<sup>8</sup> in 1938 added three cases of tuberculosis. In two there was a leukemic blood response, and in the other a monoblastic response and primary anemia. In 1940 Ulrich and Parks<sup>9</sup> described the association of a leukemic blood picture and disseminated tuberculosis. No tubercles were noted in the bone marrow of their patients. An important contribution was made by Schleicher<sup>10</sup> in 1946, who drew attention to the fre-

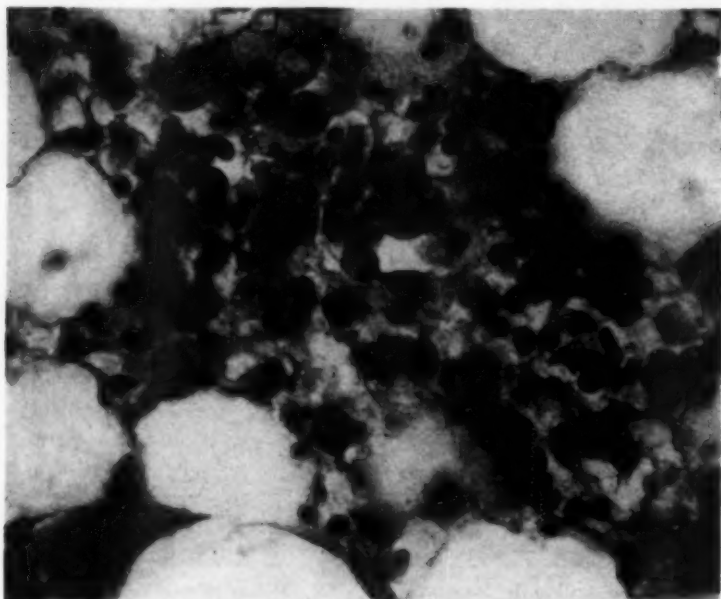


FIG. 2. Bone marrow.  $\times 500$ . Replacement of marrow elements by numerous lymphocytes, plasma cells and mononuclears.

quency of miliary tubercles in the bone marrow in hematogenous tuberculosis and suggested the use of marrow aspirations for diagnosis and prognosis. In eight cases of miliary tuberculosis he found positive bone marrows in all. Also in 1946 Chapman and Whorton<sup>11</sup> collected 37 cases of miliary tuberculosis with extra-medullary hematopoiesis. Three of the patients showed marked hypoplasia of the bone marrow; in a fourth, tubercles were present in the marrow as well. Other cases of disseminated tuberculosis associated with marked alterations in the peripheral blood picture or bone marrow have been described by Gardner and Mettier<sup>12</sup> in 1949, and Staffurth and Spencer<sup>13</sup> in 1950.



## CASE REPORT

*History:* An 82 year old white unmarried female was admitted to the hospital February 1, 1950, because of weakness of two months' duration.

Medical attention, when required, was always for a minor ailment. Therapy usually consisted of sedatives, penicillin and, intermittently, digitoxin, but no unusual drugs. Patient was described as tall, thin and energetic. In October, 1945, patient was admitted to the hospital for the nailing of a traumatic intracapsular fracture of the neck of the right femur. Laboratory data, at that time, revealed a normal urinalysis, a hemoglobin of 80 per cent, a red blood count of 4.08 million, and a white blood count of 6,750, with a normal differential. Patient was seen again at the

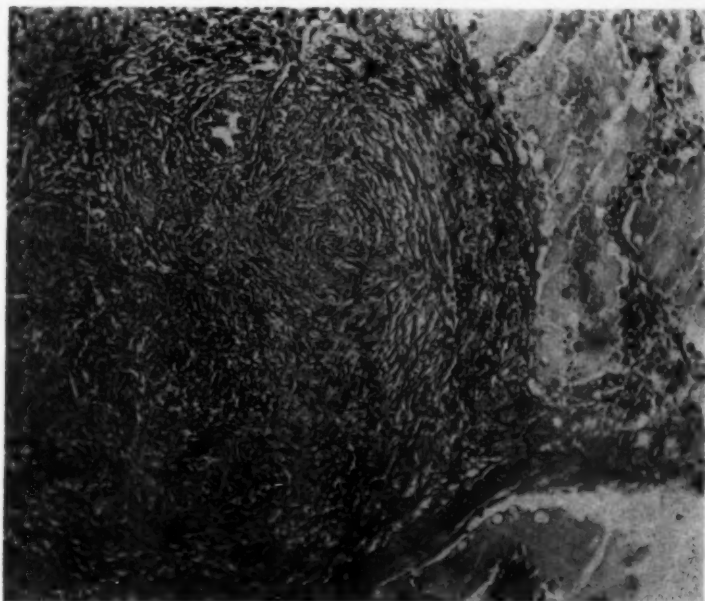


FIG. 3. Lung.  $\times 120$ . Confluent tubercles. Pulmonary edema.

hospital in February, 1948, for resection of a hammer toe of the middle digit of the left foot. The blood tests and urinalysis at this time were essentially unchanged.

Patient was said to have been well until two months preceding her final hospitalization. At this time she developed a "head cold," which improved in one week. Subsequently she failed to rally, seemed to lose ambition and was easily fatigued. Nevertheless, her appetite remained fair and she maintained her weight. At times the patient complained of vague epigastric distress. A "throat pain" became a prominent complaint but patient did not cough. It was noted that she "always raised" large amounts of thick yellow sputum, which at times was questionably mixed with blood. The patient became increasingly asthenic and a physician was summoned. A diagnosis of pharyngitis and anemia was made. Penicillin was administered but patient failed to respond and in three days she was hospitalized.



Family history is scanty, but patient's parents and three sisters were said to have died of old age. There had been no known contacts with chemicals, radioactive substances or tuberculosis.

*Physical Examination:* On admission temperature was 101° F.; pulse, 95; respirations, 20; blood pressure 140/50-0 mm. of Hg. Patient was an aged female, well developed but revealing evidence of weight loss and appearing acutely and chronically ill. There was marked pallor and also a café au lait color to her skin. Patient was restless and confused.

*Eyes, Nose and Throat:* The fundi revealed tortuosity of the vessels, with evidence of old and recent hemorrhages and fresh exudative areas. The discs were indistinct. Conjunctivae were pallid. The pharynx revealed a few scattered pe-

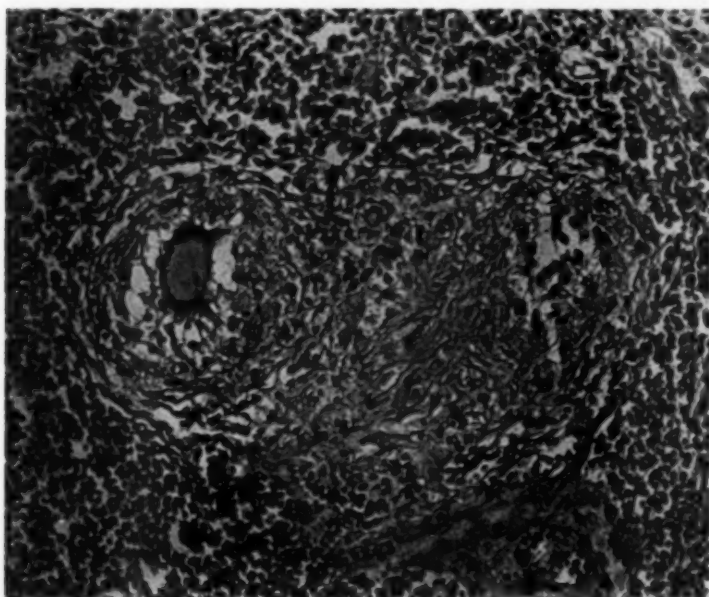


FIG. 4. Abdominal lymph node.  $\times 250$ . Miliary tubercles. Hyperplastic lymphoid tissue.

techiae. The tongue was moderately smooth about the edges. There was no adenopathy. The neck was supple.

*Chest:* The chest was symmetrical but the lungs revealed basilar râles.

*Heart:* The heart was not enlarged; a loud grade III apical systolic murmur was audible, and the heart sounds were distant and of poor quality.

*Breasts:* Negative.

*Abdomen:* The abdomen was soft and obese; no organ edges were felt.

*Rectal:* The rectal examination was negative.

*Neurologic Examination:* Neurologic examination revealed active deep tendon reflexes and no pathologic reflexes. Vibratory and position senses could not be evaluated.

*Laboratory Data:* Red blood count: 900,000 red blood cells; hemoglobin, 3.4 gm. White blood count: 800 cells, with differential revealing 13 segmented neutrophils, 7 nonsegmented neutrophils, 66 small lymphocytes, 14 large lymphocytes. There was marked poikilocytosis but no macrocytosis. Platelets, 70,000. Coagulation time, 4 minutes, (Lee-White). Clot retraction, 3.5 hours. Urinalysis, negative except for 1 plus albumin.

Wintrobe hematocrit, 6 mm. per 100 c.c. of blood; MCV 66, MCH 36, MCHC 56 per cent.

*Bone Marrow Smear:* The bone marrow revealed almost complete absence of normal bone marrow inhabitants. Only rare myelocytes were seen, almost no nucleated red cells. No megakaryocytes were found. The predominating cell was

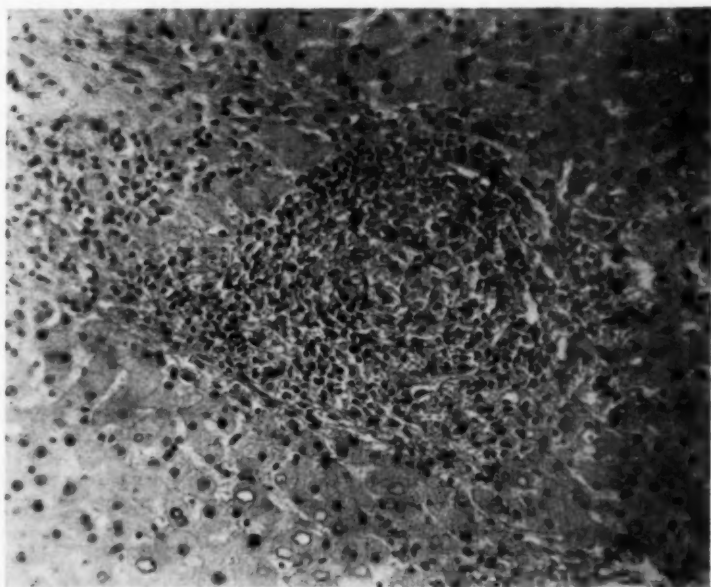


FIG. 5. Liver.  $\times 250$ . Tubercle in hepatic parenchyma.

large, with a large reticular nucleus and a curiously bright blue body within the nucleus. These cells, where preserved, had a large foamy cytoplasm. In a few foci reticular cells associated with fibroblasts were seen. Plasma cells and lymphocytes with a few bizarre blood platelets made up the rest of the picture. The marrow was consistent with that of aplastic anemia. No tubercles were present in the specimens examined.

*X-rays:* A chest film revealed questionable enlargement in the left hilar shadow. The abdominal film was not satisfactory.

*Therapy and Course:* Patient was placed on 300,000 units of procaine penicillin daily. A 500 c.c. blood transfusion was given. On the next day the patient's temperature had risen to 102.6° F.; hemoglobin was 4.5 gm.; red blood count, 1,490,000;

white blood count, 1,450. The patient's condition remained unchanged. A second 500 c.c. transfusion was given. On the next day the patient was more disoriented; temperature was 103° F. and rising. Hemoglobin, 6 gm.; red blood cells, 1,400,000; white blood count, 800 cells, 5 nonsegmented neutrophils, 15 segmented neutrophils, 64 large lymphocytes, 16 small lymphocytes. On the third day, the temperature rose to 104.6° F. Patient was completely unresponsive and quietly died.

*Autopsy Findings: External Examination:* This revealed a quite well nourished but extremely pale elderly female with a scanty beard on the chin. The pupils were equal. The abdomen showed no abnormalities. No lymph nodes were palpated externally.

*Pleural Cavities:* Fluid: right, 0; left, 75 c.c. Pericardial sac: fluid, 25 c.c. Pulmonary artery: clear. The pleural cavities were completely free from adhesions. The left cavity contained a small amount of clear yellow fluid. The pericardial cavity showed no abnormalities.

*Peritoneal Cavity:* Fluid: 0. Subcutaneous fat: 1 cm. The organs lay within their normal anatomic positions. Nothing unusual was encountered, the peritoneum being smooth and shiny everywhere.

*Heart:* The pericardium was shiny. The coronary arteries contained a severe degree of atherosclerosis. No actual occlusions were encountered. The myocardium was pale and had a yellow tint, but no evidence of old or recent infarction was seen. The papillary muscles were particularly yellow. The valves showed nothing beyond fibrous thickening of the mitral and aortic leaflets.

*Lungs:* Right lung weighed 850 gm.; the left, 910 gm. The pleurae were shiny. The pulmonary vessels were not remarkable. The bronchi contained considerable light frothy fluid. The cut surfaces exhibited everywhere severe edema and congestion, and underlying emphysema was also apparent. Both apices contained old fibrous scars, and one area in the pectoral segment of the left upper lobe had a focus of apparently active tuberculosis, measuring approximately 2.5 cm. in diameter. No enlargement of hilar or mediastinal nodes was found.

*Spleen:* Weight, 360 gm. The spleen was large, firm, dark red and deeply lobulated. The cut surfaces were solid and fairly homogeneous. Fibrous trabeculae were visible, but the Malpighian corpuscles could not be seen.

*Stomach and Duodenum:* No abnormalities were noted.

*Pancreas:* Length, 15 cm. The head and midportion were relatively soft, but the tail was rather firmer than usual. No tumor, however, was encountered grossly. Several enlarged lymph glands were found around the organ.

*Liver:* The liver was soft, pale and flabby. The cut surfaces showed nothing beyond some chronic congestion and considerable pallor.

*Gall-bladder and Ducts:* The gall-bladder contained numerous pea-sized faceted stones.

*Adrenals:* No abnormalities were seen grossly.

*Kidneys:* The renal arteries were sclerotic but quite adequate. The capsules stripped with some difficulty bilaterally, revealing a coarsely and finely scarred cortex with many small cysts. The cut surfaces revealed nothing beyond an irregular thin cortical area and extreme pallor.

*Ureters and Bladder:* No gross abnormalities were seen.

*Uterus, Ovaries and Intestines:* No gross abnormalities were seen.

*Blood Vessels and Arteries:* The aorta and other large arteries exhibited a severe degree of atherosclerosis.

*Veins:* No gross abnormalities were seen, with the exception of the fact that the left renal vein passed behind instead of in front of the aorta.

*Skeleton:* No gross lesions.

*Bone Marrow:* This was abundant, red and moist. No evidence of tumor infiltration was seen grossly.

*Lymph Nodes:* The only nodes which appeared abnormal were the para-aortic, celiac and the pancreatico-duodenal nodes; these were enlarged, the largest being in the aortic area and measuring 4 cm. across. They were soft and dark; the cut surfaces were gray and lobulated and showed many areas of hemorrhage and necrosis. A few areas in the nodes were quite hard and white.

*Microscopic:* Heart: Perivascular scarring; thickening of coronary arterioles and some atrophy of myocardial fibers.

*Lungs:* There was a focus of fibrocaseous active tuberculosis in the left upper lobe. Other sections of the lungs showed congestion and edema and areas of focal pneumonia.

*Spleen:* Congestion and discrete miliary tubercles.

*Liver:* No microscopic lesions other than a few discrete miliary tubercles.

*Pancreas:* Metaplasia of duct epithelium.

*Adrenals:* No microscopic lesions.

*Stomach and Duodenum:* No microscopic lesions.

*Kidneys:* Arteriosclerotic scars; thickening of larger vessels and retention cysts.

*Lymph Nodes:* Section of the abdominal lymph nodes revealed them to be largely replaced by confluent fibrous and caseous active tubercles.

*Bone Marrow:* The bone marrow contained fat and was hypoplastic. Scattered tubercles were present in the marrow. Here and there were accumulations of lymphocytes. The cellular portions of the marrow contained large numbers of plasma cells and lymphocytes, with very few recognizable normal elements except megakaryocytes. Numerous miliary tubercles were present in these sections.

*Final Anatomic Diagnosis:* Disseminated fibrocaseous tuberculosis with tubercles in lung, abdominal lymph nodes, spleen, liver and bone marrow. Hypoplasia of bone marrow with replacement by plasma cells and lymphocytes. Generalized arteriosclerosis. Scars of heart and kidneys. Pulmonary congestion and edema. Focal pneumonia. Metaplasia of duct epithelium of pancreas. Gall stones.

#### COMMENT

Although miliary tubercles of the bone marrow have been frequently described by pathologists, it is only in sporadic instances that the relationship between disseminated tuberculosis and such changes in the peripheral blood as pancytopenia or leukemia-like reactions has been noticed. As seen from the literature, Dyke was familiar with this association as early as 1924. Doan and Sabin produced the whole range of hematopoietic variations experimentally in 1927 and described them in detail. The significance of these experiments has largely been lost sight of from the clinical standpoint. It is also apparent from the literature that pancytopenia and leukemoid reactions probably are not the only responses of the peripheral blood marrow. Taken separately, these responses appear to have little uniformity; but judging by the experimental work of Sabin and her collaborators, if these cases could be followed throughout their courses they would probably fall into a logical sequence, parallel to the proliferative and regressive sequences described in the experimental animal.

#### SUMMARY

The literature on the association of miliary tuberculosis with changes in the peripheral blood and marrow has been summarized.

Data on a patient with miliary tuberculosis and pancytopenia have been presented.

Attention is called to the fact that this association has not been frequently recognized.

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#### CLINICAL MANIFESTATIONS OF IDIOPATHIC HYPOPARATHYROIDISM: REPORT OF ONE CASE\*

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THE scarcity of reported cases of idiopathic hypoparathyroidism is an indication of defective knowledge of the disease and of failure to recognize it, rather than an indication that it is an extremely rare affection, according to Lachmann.<sup>1</sup>

\* Received for publication September 5, 1951.

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion and policy of the Veterans Administration.

Acknowledgment is given to the Medical Illustration Laboratory Veterans Administration Medical Teaching Group, Kennedy Hospital, Memphis, Tennessee, for preparing the charts and photographs.

He reviewed a total of 70 cases reported from 1924 to 1939. To date 113 have been reported. Some of these are not positively substantiated by records. The average duration of manifestations before the diagnosis is made has been approximately nine years. We have been studying a case with manifestations of 20 years' duration before diagnosis was made. These observations tend to support Lachmann's statement.

This disease is approximately twice as frequent in females as in males, with over 50 per cent of the cases showing onset of symptoms below the age of 15 years. In the 113 cases reviewed,<sup>1-32</sup> 67 patients were females, 37 were males, and in nine cases the sex was not mentioned. The age of onset varied between two and 74, with an average of 20, but 59 per cent of the cases occurred below 15 years and 27 per cent below the age of five.

As the name implies, the etiology of idiopathic hypoparathyroidism is not known. Several theories of the relationship of infection and birth trauma have been advanced.<sup>4,10</sup> Drake, Albright et al.<sup>10</sup> have reported one case in which the four parathyroid glands, seen at necropsy, appeared grossly normal but the parenchymal cells had been completely replaced by fat. Three separate reports of idiopathic hypoparathyroidism in siblings, affecting two,<sup>6</sup> three<sup>1</sup> and five<sup>29</sup> cases, respectively, suggest that a hereditary factor may have some relationship with the development of this deficiency.

#### CASE REPORT

A 31 year old white male tire builder, first admitted to the Neuropsychiatric Service on September 15, 1947, stated that two months prior to admission he experienced the first of two episodes of loss of consciousness. The first occurred while he was painting his house; he fell to the ground and, according to his wife, was unconscious and jerking, but there was no incontinence. While still unconscious he was taken to a local hospital and given emergency therapy. He rested one day in the hospital and then returned to work. On September 14, while standing on a ladder, he fell to the ground and remained unconscious for from one to two hours. Between the episodes he had noted "sluggish spells" and the loss of about 15 pounds of weight. There was no history of headaches or head trauma. He had had 32 months of Army service, 26 of which were overseas in a combat area, without a neuropsychiatric breakdown. While in the service he had frequent nightmares and continued to have these after discharge. He and his wife had not been happy together and were considering separation. His wife described him as weak, rundown, irritable and tense.

No significant physical abnormalities were noted on examination during his first hospitalization. He appeared to be of average adult intelligence, composed and calm, but he admitted states of tension and apprehension. The laboratory findings included normal blood count, glucose tolerance test, sedimentation rate and urinalysis. Blood Kolmer was negative. Stools for ova and parasites were negative. Electrocardiogram was reported within normal limits. An electroencephalogram was reported as borderline normal, with slight dysrhythmia but no localization, and the record was not considered typical of any pathologic condition. An x-ray of the skull revealed bilateral calcifications in the region of the basal ganglia, which were interpreted as having no clinical significance. He complained of impaired vision and was seen by the ophthalmologist, who found no evidence of intraocular or intracranial disease. After rest and following some psychiatric interviews, the patient stated that he felt much improved. His weight and appetite increased, and he and his wife were reconciled. He was discharged on November 10, 1947, with the opinion expressed that

there was no space-occupying intracranial lesion and that it was unlikely that this was a case of genuine idiopathic epilepsy. (It is noted that blood calcium and phosphorus levels were ordered on November 7 but were never secured.) Discharge diagnosis was: anxiety state, chronic, moderate, manifested by general nervousness, nightmares and two episodes of fainting.

The patient was re-admitted on February 27, 1950, stating he had done very well for about one year after the previous discharge, but after that had developed tenseness and was started on barbiturates. This relieved his symptoms for several months but after that was ineffective, and Dilantin had been prescribed. This had not produced

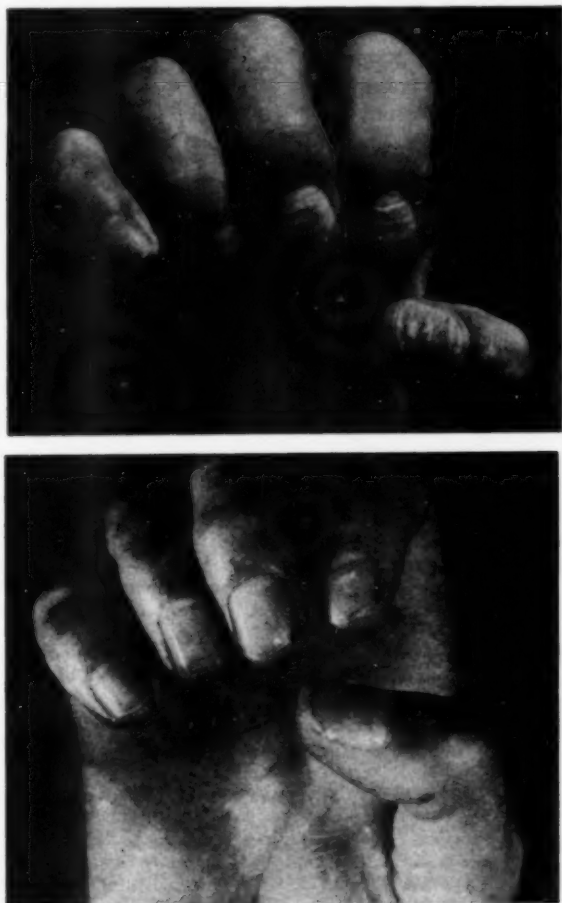


FIG. 1. (A) Horizontal ridging of nails prior to therapy. (B) Complete disappearance of horizontal ridging after therapy.



any relief; in fact, he had become worse and had noticed some tightness of muscles of his jaw and extremities, numbness in his extremities, and tenseness of neck muscles on yawning, with intermittent episodes of abdominal cramping and diminution of visual acuity. Abdominal cramping was worse after eating, especially if he ate meat.

Physical examination revealed a well developed, thin white male who appeared tense and anxious. There was some spasm of the muscles of the lower extremities on palpation, and deep tendon reflexes were hyperactive. Ridging of his fingernails was noted. There was brown pigmentation of areas of the skin over the forehead and back of the neck. Chvostek's sign was positive. Initial laboratory studies revealed normal blood counts, urinalysis, fasting blood sugar and chest x-ray. An electroencephalogram was performed before and during hyperventilation. During the hyperventilation a grand mal seizure occurred. He was referred to the ophthalmologist again because of his poor vision, and bilateral subcapsular cataracts were found. After medical consultation, the serum calcium was found to be 6.3 mg. per cent and the serum phosphorus 7.8 mg. per cent. Serum alkaline phosphatase was 5.8 King-Armstrong units. The diagnosis of probable idiopathic hypoparathyroidism

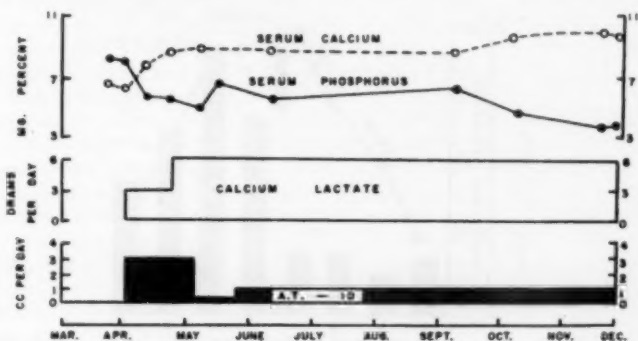


CHART 1. Graphic illustration of the serum calcium and phosphorus response to calcium lactate and AT 10 therapy.

was made. The patient was then transferred to the Medical Service where, because of his brownish pigmentations and the reported association of Addison's disease with idiopathic hypoparathyroidism,<sup>28</sup> a 17-ketosteroid determination and a water test were performed. These tests were normal. Daily Sulkowitch's tests showed no precipitation of calcium in the patient's urine. The marked ridging and brittleness of the patient's fingernails disappeared on therapy (figures 1 A and 1 B). Reexaminations of the skull by x-ray on April 3, 1950, and in March, 1951, revealed the basal ganglion calcification to be unchanged. X-rays of other bones have shown no significant changes.

An electrocardiogram taken on March 10, 1950, showed prolongation of the Q-T interval (0.52 second), with depression and straightening of the S-T segment. The calculated normal Q-T interval was 0.39 second. Repeat electrocardiogram on April 24 showed a Q-T interval of 0.42 second.

Treatment with a high calcium and low phosphorus diet, calcium lactate and dihydrotachysterol was begun (chart 1). Within one week the patient's symptoms had shown marked improvement and his urine showed calcium (Sulkowitch's test). The patient became ambulatory with no symptoms other than impaired vision.

On January 9, 1951, a tonsillectomy was performed. On January 16 an intracapsular cataract extraction with peripheral iridotomy was performed on the left eye, and on January 21 simple intracapsular cataract extraction on the right eye was performed. The postoperative course was uneventful and no different from the usual postoperative picture. During this period the patient continued to receive 2 dr. of calcium lactate three times a day and 1 c.c. of Hytakerol six days a week.

An Ellsworth-Howard test was performed on March 10 to demonstrate the normal or increased response to parathyroid hormone that true hypoparathyroid patients exhibit, in contrast to the lack of response shown by pseudohypoparathyroid patients. The patient was fasting and at bed-rest. His phosphorus excretion increased approximately fourfold after the injection of parathyroid extract\* (chart 2). Two cubic centimeters of the extract were diluted with 8 c.c. of saline and given intravenously. This was scheduled to be given at 10:00 a.m. but was delayed until 10:45 a.m. because of a fairly marked reaction to the intradermal test. Comparison with intradermal reactions on four controls at that time revealed that this was the normal

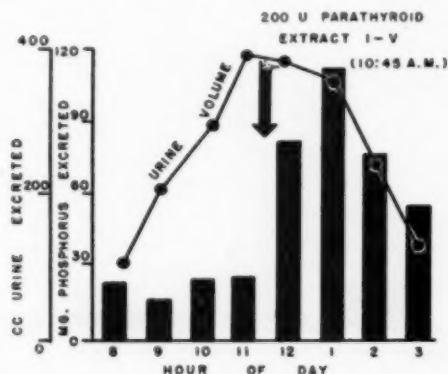


CHART 2. Graphic illustration of the Ellsworth-Howard test. Note that there was approximately fourfold increase in the urinary phosphorus excretion following parathyroid extract intravenously.

response and the drug was then administered. The patient's therapy has since been continued unchanged, and he has had no symptoms other than those of impaired vision.

Further investigation has revealed that in 1941 the patient had been hospitalized for study but the diagnosis of hypoparathyroidism had not been made. He complained of cramping in his legs, hands and abdomen of 10 to 15 years' duration. Serum calcium was found to be 6.6 mg. per cent and phosphorus 6.8 mg. per cent. While in service in the Southwest Pacific he developed acute appendicitis. Records made then reveal that carpal spasm was found and 20 c.c. of calcium gluconate solution were given intravenously before the spasm disappeared. His postoperative course was uneventful and he was returned to duty.

#### DISCUSSION

The clinical manifestations of idiopathic hypoparathyroidism are quite similar to those of postoperative parathyroid insufficiency. They differ primarily in that

\* Parathyroid Extract—Lilly.

tetany may be more latent and that the trophic changes are more pronounced due to the chronicity of the disease.

*Nervous System:* Tetany, although not always the first, is the most common symptom noted in cases of idiopathic hypoparathyroidism. Of the 113 cases reported in the literature, 76 showed some form of tetany. Often latent tetany will appear during menstrual periods, demonstrating the antagonistic relationship of the ovary and parathyroid glands.<sup>13, 15, 20</sup> The tetany of parathyroid insufficiency is no different from that due to hypocalcemia of any cause. There may be paresthesias, cramps, and muscle spasms of the arms, hands (accoucheur's hand), legs and, rarely, the facial muscles. Often laryngeal spasm and bronchial spasm will be the only symptoms, especially in infants. When gastric tetany produces severe abdominal cramps, a gastrointestinal disorder or acute surgical intraabdominal condition may be suspected.

Epilepsy may or may not accompany tetany. Although epilepsy in this disease is primarily due to the hypocalcemia, other factors such as the mineral content of diet, edema and stress are important. McQuarrie et al.<sup>25</sup> showed that in patients on a low mineral diet the convulsive tendency increased following Pitresin, and also after fever induced by typhoid vaccine, although serum calcium and phosphorus remained at a constant level; whereas, under similar conditions, the convulsive tendency decreased in patients on a high mineral diet. It was his opinion that, in addition to the decreased concentration of the calcium ion in the extra-cellular fluid, there was edema of the brain with abnormal electric potentials produced by the disturbance in the surface function of the membrane of the brain cell. In some rare cases, increased spinal fluid pressure and papilledema may accompany the epilepsy, presenting the clinical picture of a brain tumor.<sup>4, 10</sup> Barr et al.<sup>3</sup> reported a case with a spinal fluid pressure of 350 mm. of water. He theorized that, since the spinal fluid calcium remains constant,<sup>7</sup> the differences in the concentration of the two sides of the membrane may contribute to the formation of the cerebral and meningeal edema. Berezin and Stein<sup>4</sup> report a case of an eight year old male diagnosed as petit mal complicated by hypoparathyroidism at the age of five. At the age of six, because of papilledema and increased spinal fluid pressure persisting after the chemistry returned to normal following therapy with vitamin D and calcium chloride, a ventriculogram was done and found to be normal. Therapy was continued and when the patient reached the age of eight the papilledema had disappeared. They recommended that calcium and phosphorus determinations be made before the diagnosis of idiopathic epilepsy is made or before an operation for brain tumor is performed.

Although the incidence of grand mal seizures with hypoparathyroidism varies, and although some reports show a high incidence, the fact remains that these are a select group investigated because of hypocalcemia and not because of epilepsy. The serum calcium in idiopathic epilepsy varies considerably and is of no value in the diagnosis per se. Lachmann<sup>1</sup> concluded, after examining a large number of persons with supposed idiopathic epilepsy, that there may be a few with hypoparathyroidism who will respond dramatically to the antitetanic therapy. In the present review, 36 cases of hypoparathyroidism with grand mal seizures have been collected.

The electroencephalogram shows a tendency for the slow alpha rhythm to diminish or disappear in the frontal, occipital and parietal leads. There will be

increase in amplitude and constancy of the beta rhythm, appearing uniformly, paroxysmally or as a modulating alpha rhythm. There is an increase in the waves of low frequency, two to five per second, with small spikes sometimes appearing along with waves of a frequency of six to seven per second.<sup>16, 22</sup> Odoriz et al.<sup>23</sup> found that hyperventilation caused no changes in the electroencephalogram of normal individuals but produced the above changes in cases of hypoparathyroidism in which the base electroencephalograms were normal. In those cases initially showing some abnormality, there was exaggeration following hyperventilation. Following therapy, the pattern may or may not return to normal.<sup>21, 22</sup>

Mental retardation and mental disturbances may be the first signs of idiopathic hypoparathyroidism. This has been most frequently associated with postoperative insufficiency, because of the sudden onset of tetany with inability of the brain cells to adjust to the acute chemical changes.<sup>24</sup> Although there may be no improvement in the psychologic status after therapy,<sup>25</sup> Greene and Swanson<sup>26</sup> state that the acute mental disturbances never recur after therapy, even though tetany and convulsions may continue. Because of the association of hypoparathyroidism and mental retardation, Weber<sup>26</sup> recommended that x-rays of the skull be taken in all cases of mentally retarded children in search for the calcification of basal ganglia frequently seen in hypoparathyroidism. Although mental disturbances are frequent, true psychosis rarely develops. Disturbances of minor degree consist of headaches, irritability, depression and dizziness, often leading to the erroneous diagnosis of psychoneurosis or hysteria when tetany is not marked.<sup>1, 2</sup> The patient presented in this report graphically illustrates irritability and personality changes accompanied by significant spasm, but, due to the lack of appreciation of the association of hypoparathyroidism with these clinical features, he was labelled psychoneurotic for many years.

Isolated paresis is extremely rare, having been reported only once.<sup>1</sup> That patient had transient paresis of one extremity and then another. With the institution of therapy in the form of dihydrotachysterol, the paresis subsided promptly.

*Trophic Changes in Ectodermal Tissue: Hair:* There may be complete loss of hair in the acute exacerbations of chronic tetany, but diffuse thinning is more common in parathyroid insufficiencies.<sup>1, 19, 27</sup>

*Skin:* The types of skin changes in idiopathic hypoparathyroidism are multiple and most often cannot be differentiated from other skin diseases. There may be vesicles, bullae, papules and eczema. Lachmann<sup>1</sup> goes into great detail concerning the relationship between impetigo herpetiformis and parathyroid insufficiency. Other observers, however, have not reported the association of impetigo herpetiformis and parathyroid insufficiency. Rare cases of exfoliative dermatitis have also occurred. Learner et al.<sup>27</sup> reported a case of a 50 year old female with postoperative hypoparathyroidism having pigmentation of the arms and a purplish red, sharply demarcated dermatitis on the trunk. The color and appearance of this dermatitis resembled those of pellagra but differed in location, in the beneficial response to sunlight, and in the absence of neurologic and gastrointestinal signs. Lachmann<sup>1</sup> collected two cases of idiopathic hypoparathyroidism with pigmentation and reported three of his own with pigmentation of the face resembling chloasma gravidarum. In some rare cases there has been the association of Addison's disease with hypoparathyroidism. Leonard,<sup>28</sup> in a

review, found only two cases with Addison's disease and added one of her own, all occurring in children.<sup>29, 30</sup> In Leonard's case, autopsy findings revealed no evidence of parathyroid glands and absence of the adrenal cortical tissue. That was the only case of proved adrenal cortical atrophy associated with idiopathic hypoparathyroidism. In the other two cases, no adrenal cortical atrophy was noted.<sup>2, 10</sup>

**Nails:** There have been reports of complete loss of nails during episodes of chronic tetany of all types, including hypoparathyroidism.<sup>1, 37</sup> It is more common for ridges to develop on the nails of the hands and feet. The nails become white and crumbly and the nail plates separate. The nails become sharp, thick and overgrown by skin.<sup>12</sup> Horizontal grooving of the nails, with thinner, less prominent longitudinal grooves, is said to be typical. Although some authors report the association of hypoparathyroidism and moniliasis,<sup>9, 18, 20</sup> it is unlikely that the nails of the two conditions will be confused. Nail changes will rapidly disappear following therapy, as demonstrated in the photographs of the hands of the patient presented.

**Eye Lenses:** Albright<sup>38</sup> states that lenticular changes or true cataracts occur in almost all cases of longstanding hypoparathyroidism, idiopathic and post-operative alike. Lachmann<sup>1</sup> found cataracts in one-third of all of his patients reported, and in four-fifths of those in whom pronounced deficiency for a considerable length of time was noted. Forty of the 113 cases reviewed had cataracts. Although some authors have suggested that cataracts are due to the convulsions with ciliary spasm, it is now believed that the cataracts are due to the low serum calcium, since cataracts can occur in other conditions without convulsion and with a low serum calcium and normal serum phosphorus.<sup>12, 39</sup> The opacities are subcapsular, first noted beneath the posterior capsule, and spread with raylike opacities extending to the anterior capsule. There is an accompanying flattening of the AP diameter of the lens.<sup>39, 40</sup> Variations of the opacities are noted, probably due to the degree of insufficiency. In some cases lenticular changes are often arranged in layers, alternating with layers of normal tissue. This is probably due to periodic exacerbations of parathyroid insufficiency or exacerbations of hypocalcemia. In the cataracts due to parathyroid insufficiency, the embryonal nucleus is never affected. Creutzburg<sup>40</sup> also emphasizes the vascular spasm of the retinae and optic tracts that can lead to continual disturbance of vision. In the event hypoparathyroidism is suspected, it is essential that the examination be performed with a slit lamp, for early lenticular opacities cannot be visualized with the ophthalmoscope alone.<sup>1</sup> The growth of the cataracts is most often stopped when treatment is instituted, but in rare cases it continues. It is only in the very rare case that there is even slight improvement with therapy.<sup>41</sup>

**Teeth:** If parathyroid insufficiency develops in early life, defects of the enamel and dentin are usually found in the canines and incisors on the labial surface. Humans develop spotting somewhat similar to that occurring in parathyroidectomized rats. Yellow, deeply set spots, corresponding to hyperplasia of enamel, develop.<sup>42</sup> As these spots coalesce, a line or horizontal ridge forms. There are bands of normal dentin alternating with bands having a coarsely granular matrix. In some cases there is absence of enamel of the entire free end of the crown, with dentin becoming superficial. Teeth may be involved at any time of life,

becoming sensitive and showing eroded edges. Besides the defects of the enamel formation, there are delay, irregular eruption and increased density of the deciduous teeth and retarded development of the permanent teeth.<sup>12</sup>

**Electrocardiographic Changes:** Cardiac manifestations are usually those of a neurosis, including palpitation, vague pains around the heart and anxiety. These are of no value in establishing the diagnosis of idiopathic hypoparathyroidism. The electrocardiogram, on the other hand, is of much aid, due to the prolongation of the Q-T interval with flattening of the S-T segment seen in conditions with

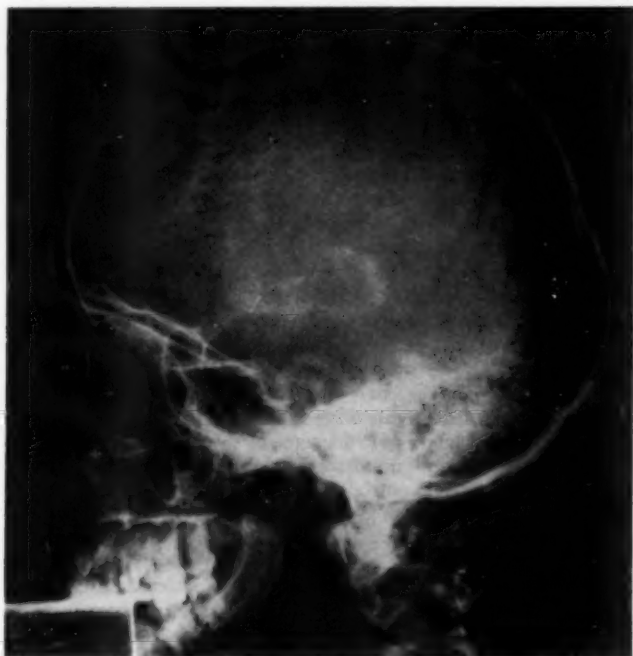


FIG. 2. Lateral view of skull showing anterior placement of the calcifications in the basal ganglia.

hypocalcemia. In some cases, however, hypocalcemia can occur and have no effect on the electrocardiogram.

**Roentgenographic Changes:** Eaton and Haines,<sup>11</sup> Kowallis,<sup>21</sup> Siglin et al.<sup>22</sup> and Camp<sup>8</sup> have reviewed the cases of idiopathic hypoparathyroidism at the Mayo Clinic. Of a total of 17 cases, 11 showed cerebral calcification, most frequently noted in the region of the basal ganglia. One of these cases also had subcutaneous calcification, most frequently seen in pseudo-hypoparathyroidism. Five of these also had diffuse cerebral cortical calcifications, and seven had accompanying cerebellar calcification. Camp stressed the importance of the lateral



as well as AP film of the skull to aid in distinguishing the calcification of basal ganglia from the calcification of choroid plexus. Calcifications of the basal ganglia have an anterior position on the lateral film, whereas choroid calcifications of the choroid plexus are noted in the region in the genu of the lateral ventricle (figure 2).

Disturbances of the cerebral metabolism lead to the deposition of colloid around the small cerebral arteries and later calcification of the colloid.<sup>5, 42</sup> It is thought that the supersaturation of the blood causes a deposition of calcium phosphate in the abnormal tissue. The calcified areas coalesce to form perivascular sheets. Although when considered with the entire clinical picture of hypoparathyroidism these calcifications are of great diagnostic significance, when taken alone they are not pathognomonic. These calcifications can occur in mental deficiency, idiopathic epilepsy, Virchow's interstitial encephalitis, chronic lead poisoning, tuberculous meningitis, schizophrenia, carbon monoxide poisoning, tropical malaria, chronic alcoholism and tuberous sclerosis.<sup>5, 11, 44</sup> Idiopathic hypoparathyroidism should always be considered in those cases in whom no other cause is present. In these cases with cerebral symptoms and calcification due to idiopathic parathyroid insufficiency the symptoms disappear with treatment, although the calcifications remain present. This demonstrates that the calcifications in these cases are a result of the parathyroid insufficiency and not the cause of the central nervous system symptoms.

#### TREATMENT

Treatment consists of measures designed to increase serum calcium and reduce serum phosphorus. A high calcium and low phosphorus diet, which restricts intake of milk and milk products because of their high phosphorus content, is used with supplemental calcium chloride, gluconate or lactate. Aluminum hydroxide has been used to decrease phosphorus absorption, but it is ordinarily not necessary. Either vitamin D in large doses or dihydrotachysterol (AT 10) is used. The former increases both calcium absorption and phosphorus excretion. Parathyroid hormone is not used because of the development of "resistance" to this after usage over long periods.

#### SUMMARY

1. Idiopathic hypoparathyroidism is a rarely diagnosed state, probably due to defective knowledge of the disease and failure to recognize it. The average duration of manifestations before diagnosis has been about nine years.

2. A case is presented with about 20 years' duration of symptoms before diagnosis was made.

3. Clinical manifestations are reviewed in detail and treatment is outlined briefly.

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## ABSCESSSES OF MYOCARDIUM DUE TO SUPPURATIVE MEDIASTINAL DERMOID: ANGIOCARDIOGRAPHIC AND PATHOLOGIC STUDY \*

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ABSCESS of the myocardium is rare and usually associated with septicemia. Flaxman<sup>1</sup> found 29 instances in 14,160 autopsies, an incidence of 0.2 per cent. Saphir<sup>2</sup> reported upon 32 myocardial abscesses occurring in 5,626 autopsies, an incidence of 0.6 per cent. Tubercles<sup>3</sup> have invaded the myocardium, presumably also as a result of hematogenous dissemination. Abscess formation has occurred in myocardial infarcts complicated by pneumonia with septicemia.<sup>4</sup> Direct extension of granulomatous lesions from lung or chest wall in actinomycosis,<sup>5</sup> extension to the heart from tuberculous pericarditis<sup>6</sup> and myocardial involvement by Boeck's sarcoid<sup>6</sup> have been encountered. In most instances, cardiac abscess occurs as part of a more widespread systemic disease. Myocardial abscess formation due to direct extension from a contiguous dermoid cyst, such as occurred in the case reported below, is a rare, possibly unique occurrence.

### CASE REPORT

A 31 year old white female was first admitted to Morrisania City Hospital on January 11, 1951, with a diagnosis of bacterial endocarditis and septicemia. For two months she had noted the presence of malaise and fever, the latter usually occurring in the evening and occasionally accompanied by chills. This continued until admission.

The patient had had good health until the age of 23, eight years prior to her admission. She had been an active, athletic girl, was considered a "tom-boy," and had participated in competitive sports without difficulty. Following the birth of her only child, eight years before, she had complained of weakness and flatulence, attributed to anemia and gall-bladder disease. She also noted mild, fleeting joint pains, but at no time were her joints red or swollen. Six years before admission and several months following an attack of acute tonsillitis her tonsils were removed, but the joint pains recurred intermittently. At the age of 27, four years before admission, she developed malaise and an intermittent fever which persisted for several weeks. On the basis of cardiac murmurs a diagnosis of subacute bacterial endocarditis was entertained, although the only blood culture taken was negative. She received a 10 day course of penicillin, following which her temperature returned to normal. Chest x-ray at that time revealed a rounded, circumscribed shadow in the region of the pulmonary artery (figure 1), the nature of which was not determined but which was assumed to represent pulmonary artery enlargement due to cardiac disease.

Following this episode, she continued to complain of fatigue and shortness of breath with mild effort. For two years thereafter she was advised to limit her activity and so spent much of her time in bed. She was told that she had either congenital or rheumatic heart disease. Although she gradually increased her activity, performing milder household duties, she did not attempt to climb stairs and was carried to and from the street in a chair. Had her condition been correctly

\* Received for publication August 18, 1951.

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diagnosed at this time, adequate surgical therapy might have brought about complete cure.

Ten weeks prior to her hospitalization, malaise and fever recurred and persisted. For 10 days before admission she was given penicillin, without effect. Pain and cough were not symptoms.

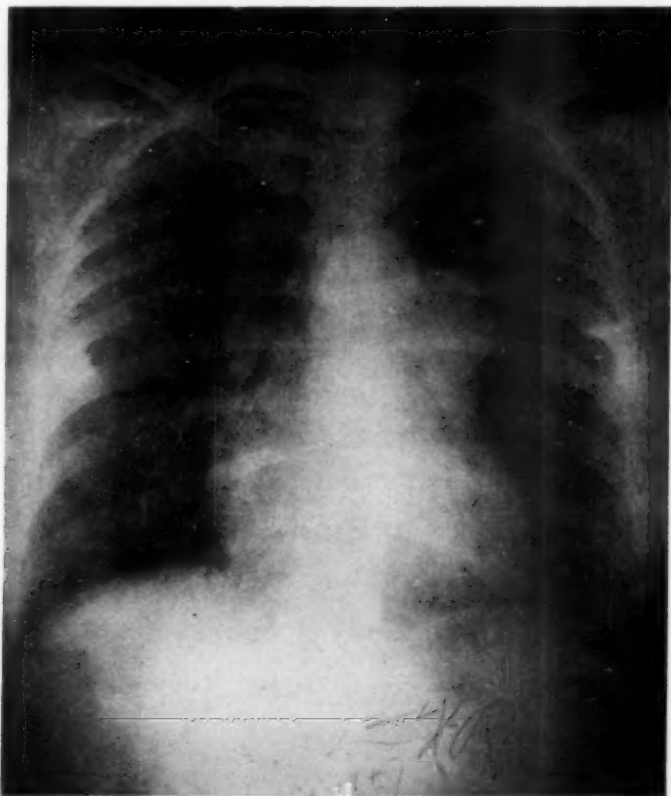


FIG. 1. Conventional roentgenogram made four years prior to final hospital admission. The left hilar density was interpreted as an enlarged pulmonary artery associated with either rheumatic or congenital heart disease.

On admission the patient appeared to be comfortable and not acutely ill. The temperature was 100° F.; the pulse, 100, regular and of good quality; the blood pressure, 120/70 mm. of Hg. Pertinent physical findings were confined to the chest. There was marked widening of the area of dullness at the base of the heart extending to the left, and also of the cardiac area itself, extending to both right and left. The upper left precordium was prominent, and pulsation could be seen and felt over this

area. A short, rough, grade III blowing systolic murmur was present over the entire precordium, with greatest intensity at the pulmonic area. The murmur was also audible posteriorly on the left.

Chest roentgenograms (figure 2) showed a much larger shadow than had been present four years earlier. The cardiac silhouette was greatly widened to the right and left. On lateral projection, a shadow was seen to lie anterior to the heart.



FIG. 2. Roentgenograms made at time of final hospital admission. A. Frontal film showed enlargement of the mass in the pulmonary artery region and along the left heart border.

Electrocardiography showed inverted  $T_1$  and depressed  $ST_{2-3}$ ; Q, raised ST, and inverted T in  $aV_L$ ; Q in  $V_{2-3}$ ; raised ST in  $V_{1-2-3}$ , and inverted T in all V leads (figure 3). These changes were interpreted as being consistent with an antero-septal myocardial infarction. Urinalysis revealed a specific gravity of 1.014, with a trace of albumin and 3 to 4 white cells. There were no red cells. Serologic test for syphilis was negative. Hemoglobin was 10.0 gm. and the white blood cell count

was 17,300, of which 90 per cent was of the polymorphonuclear series. Daily repeated blood cultures were negative. (The patient had received penicillin for 10 days prior to her admission.) On the fifth hospital day, penicillin therapy was re-instituted, one million units every three hours. There was no response, judging by the temperature curve, her fever remaining at levels of 100° to 101° F. The patient said she felt better but expressed fear that she would die suddenly because of "heart trouble."

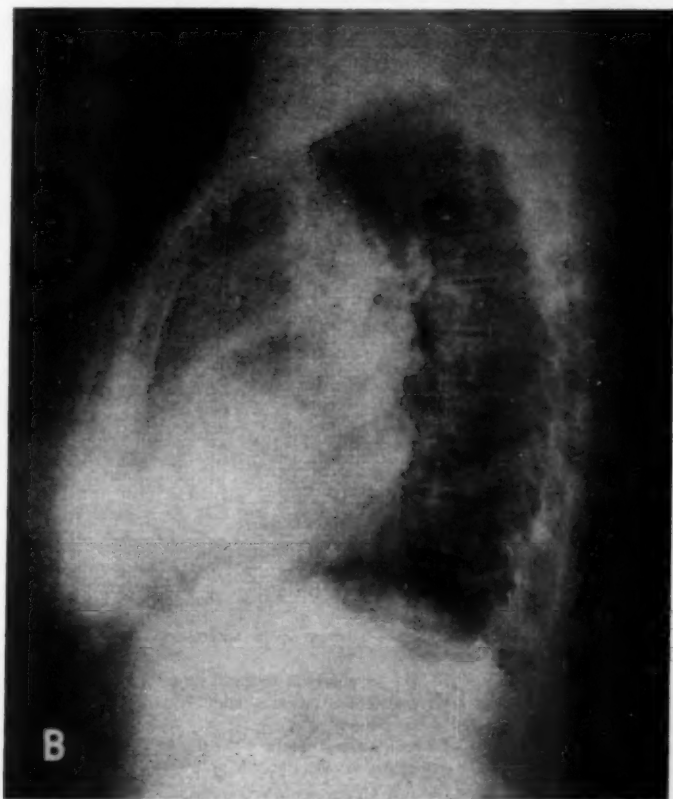


FIG. 2. B. Lateral projection demonstrated the anterior location of the mediastinal mass.

On January 23, 1951, angiocardiographic examination was conducted at The New York Hospital. Frontal and lateral studies (figures 4 and 5) indicated the presence of a large nonvascular mediastinal mass related to and displacing the heart. Because of marked cardiac and great vessel displacement, a malignant mediastinal tumor was suspected. The previously described electrocardiographic changes were thought to be due to myocardial invasion. Surgical exploration was recommended.

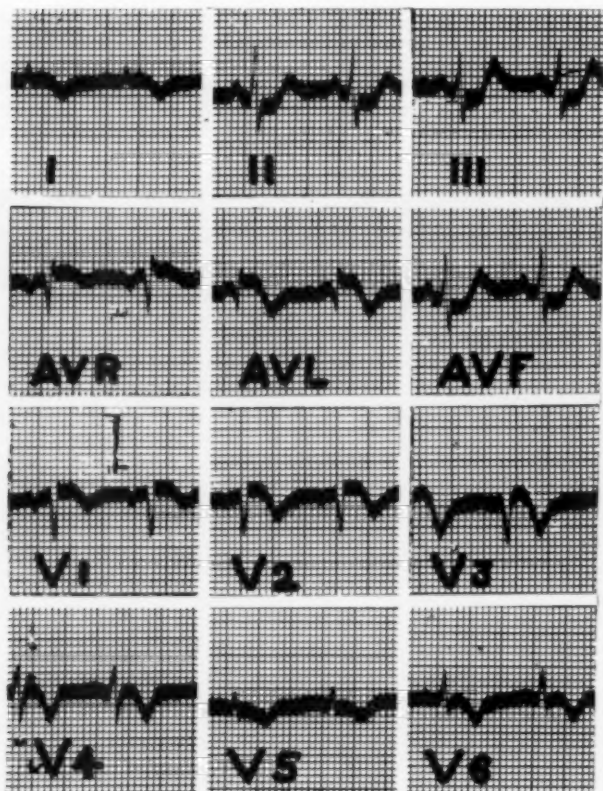


FIG. 3. Electrocardiogram showing the pattern of an anteroseptal myocardial infarction.

At 3 p.m., January 27, 1951, the seventeenth hospital day, while engaged in casual conversation with the house physician, the patient suddenly complained of dizziness, fell back in her bed and died immediately.

Autopsy was performed 18 hours after death.

#### AUTOPSY

*Gross Findings:* When the chest was opened a large, tense but fluctuant cystic tumor was found to lie beneath and adherent to the sternum. It completely covered the heart and great vessels, displacing these structures to the right, and when opened was found to contain thick, oily, greenish, purulent material which was nonodorous. This did not have the appearance of ordinary pus. The tumor was twice the size of the heart and was tightly adherent to the right ventricle over an oval-shaped area, the long axis of which lay to the right of and roughly parallel to the inter-ventricular septum. The tumor was also adherent to other parts of the heart and



to the left lung, but these adhesions were of loose connective tissue and were separated without undue difficulty. The wall of the cystic tumor was shaggy and irregular, measuring from 5 to 8 mm. in thickness. In addition to the oily fluid described above, there were also inspissated grumous material and a clump of hair within the tumor.

The heart was not enlarged; its chambers were proportionate. The valves were normal; the coronary vessels were patent, of normal caliber and consistency. A soft 10 mm. thrombus was attached to a small area of endocardium in the apical portion of the right ventricle, and beneath the thrombus was a small area of acute endocarditis. Beneath this area of endocarditis was a small, pus-containing myocardial abscess, lying within the myocardium. A probe could be passed from this abscess cavity

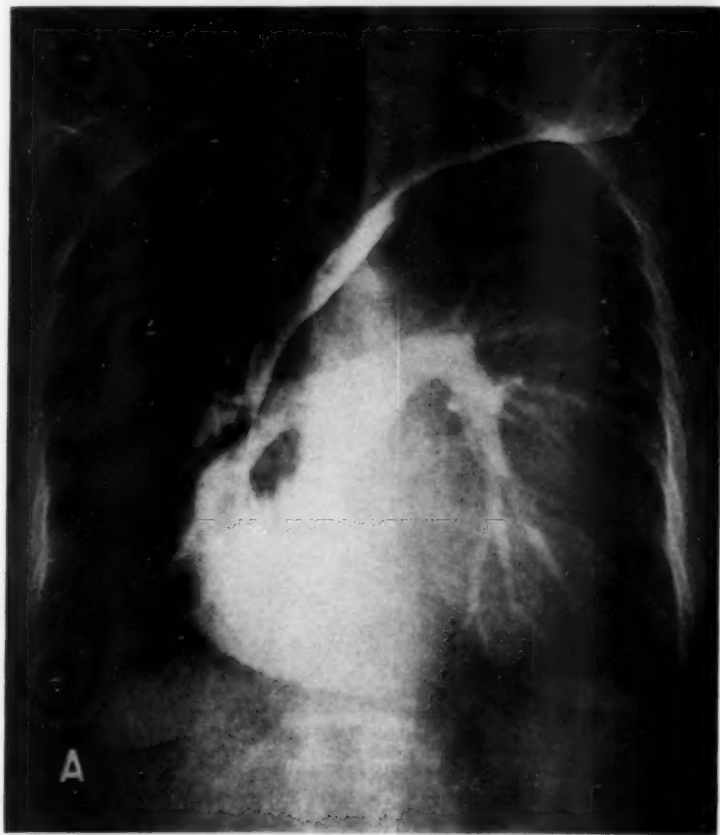


FIG. 4. Frontal angiocardigram. A. Right heart filled, superior vena cava markedly displaced laterally. Right ventricle and pulmonary conus compressed and left pulmonary artery elevated and pushed medially.

through a fistula which traversed the adherent portion of the tumor and entered its cystic cavity (figure 6).

Cut sections of the myocardium exposed numerous small abscesses in the right ventricular wall, the apical portion of the left ventricle and the apical portion of the interventricular septum. The largest of these abscesses, 4 and 5 mm. in diameter,



FIG. 4. B. Left heart and aorta opacified. Left ventricle deformed and ascending aorta displaced anteriorly. Extracardiac nature of mass clearly demonstrated.

were in the interventricular septum. The lungs and the pulmonary vessels were unremarkable, as was the remainder of the gross examination.

*Microscopic Findings:* The cyst wall contained areas of squamous epithelium, hair follicles, muscle fibers and sebaceous glands (figure 7A), and was studded with innumerable small acute abscesses (figure 7C). The myocardial abscesses showed

characteristic acute suppurative changes, with fragmentation of heart muscle and interstitial edema and cellular infiltration (figure 7C).

**Bacterial Cultures:** A nonhemolytic streptococcus, *Aerobacter aerogenes* and *Bacterium coli* were cultured from the cyst contents. It is assumed that postmortem contamination had occurred during the 18 hours between the time of death and



FIG. 5. Lateral angiogram. A. Right heart and pulmonary arteries filled. Retrosternal location of tumor visualized and resultant deformity of superior vena cava, right ventricle, pulmonary conus and pulmonary arteries shown.

autopsy. Direct smear of the cyst contents revealed no organisms, but contained innumerable polynuclear leukocytes.

**Anatomic Diagnosis:** (1) Infected dermoid cyst of anterior mediastinum, with sinus tract communicating with abscess in the myocardium. (2) Multiple myocardial abscesses involving apical portions of the right and left ventricles and the interventricular septum (acute suppurative myocarditis).

## COMMENT

Myocardial abscess formation due to direct extension from an infected dermoid cyst as exemplified by this case to our knowledge has not been described previously.

Dermoid cysts of the mediastinum probably arise from remnants of the third and fourth branchial arches, being drawn into the thorax with the descent of

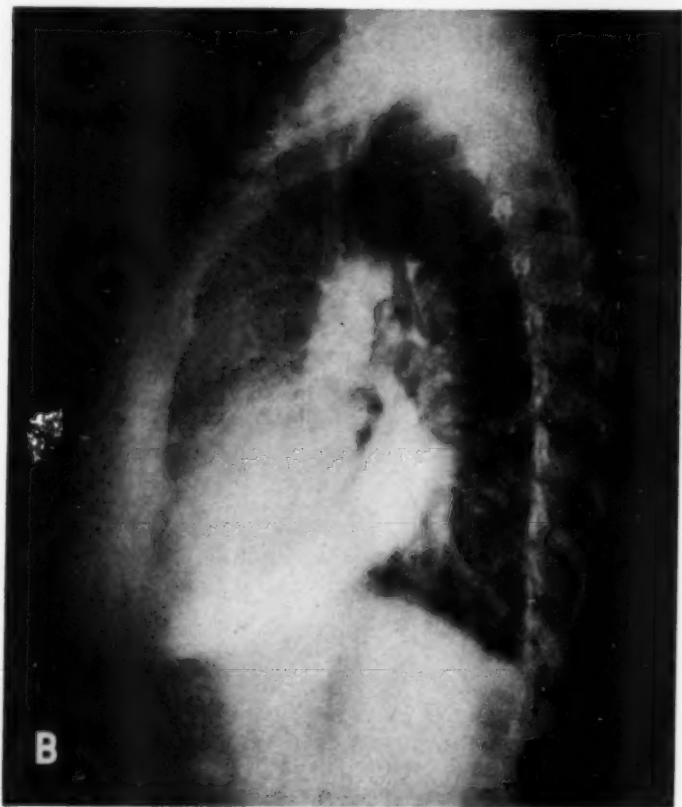


FIG. 5. B. Left heart and aorta opacified. Deformity of left ventricle and pressure against ascending aorta by tumor may be recognized.

the diaphragm and heart. Their usual anterior position supports this view. They may remain dormant until the second or third decade of life, then begin to enlarge. Endocrine changes of puberty and infection, particularly in the respiratory tract,<sup>7,8</sup> are believed to be the initiating factors. The symptomatology of dermoid cysts is dependent upon the rapidity and degree of enlargement, with

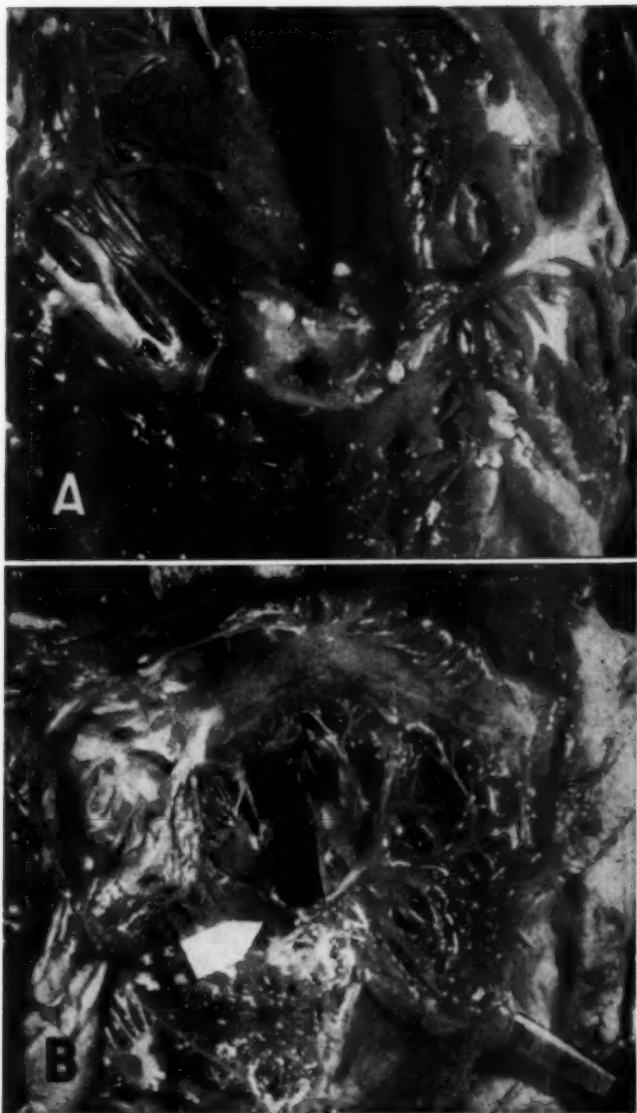


FIG. 6. Gross findings. A. Abscess in the wall of the right ventricle (opened post-mortem). Above the abscess can be seen a small area of endocarditis upon which a friable thrombus was attached. B. Probe through the fistulous tract between the cyst (right) and the myocardial abscess (arrow).

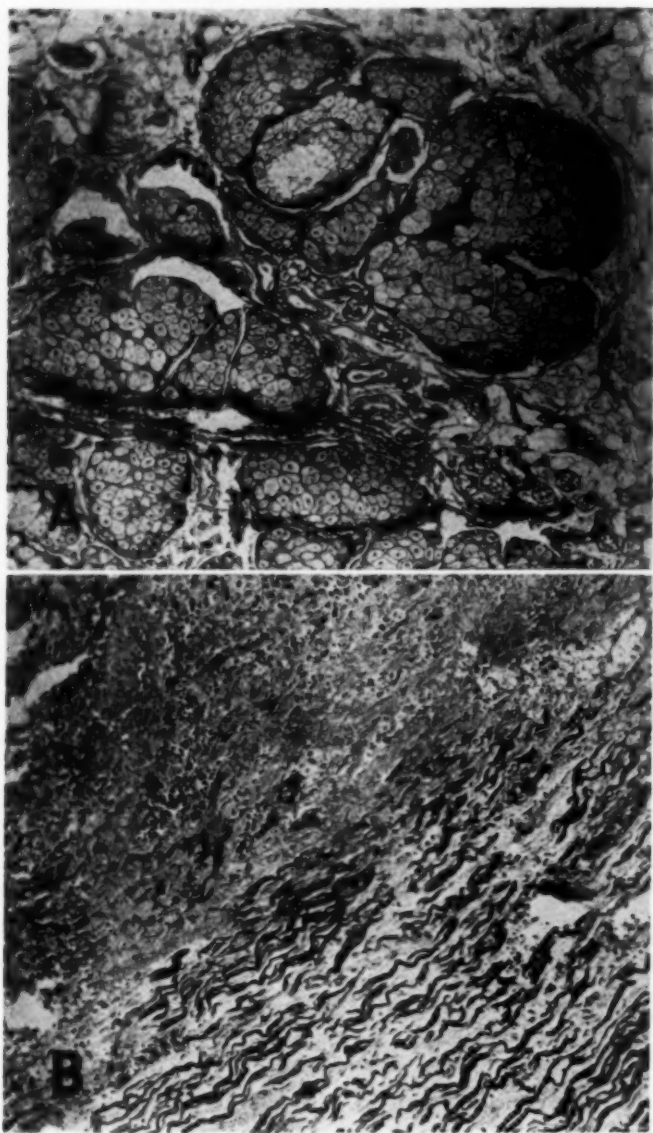


FIG. 7. Microscopic findings. A. Sebaceous glands in cyst wall. B. Myocardium with suppurative necrosis.

consequent pressure upon and displacement of mediastinal structures. Cough and pain, which are frequently described, were not present in our patient. Dyspnea on effort, another common complaint, was the outstanding symptom in this case and was probably due to pressure upon the heart, with encroachment upon the cardiac chambers, pulmonary conus and artery. The loud murmur, with maximal intensity at the pulmonic area, may also be explained by pressure at this site.

The shadow of the tumor seen on x-ray was originally thought to represent an enlarged pulmonary artery. On the basis of fever and cardiac murmur, subacute bacterial endocarditis secondary to rheumatic or congenital heart disease



FIG. 7. C. One of the numerous small abscesses that studded the cyst wall.

was suspected. Routler and Combet<sup>9</sup> report a dermoid cyst that was interpreted as an aneurysm of the pulmonary artery. Here, angiocardiology led to the correct (although incomplete) diagnosis of tumefaction.

Fever and leukocytosis are ominous signs of infection of a mediastinal dermoid. Its occurrence is attributed to infection elsewhere in the body, particularly in the respiratory tract. Rapid enlargement of dermoids has been noted to occur following respiratory infections.<sup>10</sup> When a fistula between the cyst and the bronchial tree is produced, infection is the rule. In such cases sebaceous material and hair are frequently expectorated and are diagnostic.<sup>11</sup> However, infection in the dermoid may occur without a fistulous communication, the infecting agent probably reaching the tumor via the blood stream.<sup>7</sup> Once infection



takes place, the prognosis becomes guarded. Not only do pressure phenomena become greater because of the enlarging tumor, but adhesions to surrounding structures also are more prone to occur, making surgical removal difficult.<sup>6</sup> Rupture of the tumor into neighboring structures may take place. Such an occurrence may be catastrophic.<sup>7</sup> Rusby<sup>7</sup> mentions four reports from the literature in which dermoids ruptured their contents into the pleural cavity, the pericardium, the superior vena cava and the aorta.

The clinical course in the patient reported here followed the usual pattern of infected mediastinal dermoids, with the exception of the cardiac involvement and sudden death. Nonspecific electrocardiographic changes have resulted from invasion of the myocardium by tumor,<sup>12,13</sup> parasitic infestation,<sup>14,15</sup> granulomatous lesions<sup>3</sup> and suppuration.<sup>16</sup> The electrocardiogram in this case depicted necrosis of the anteroseptal portions of the myocardium, which proved to be the case. The necrosis, however, was due to suppuration rather than infarction following coronary occlusion. The terminal episode may have been ventricular fibrillation or cardiac standstill, common causes of sudden death<sup>17</sup> which are attributed to a hyperirritable myocardium of anoxic or infectious origin.<sup>18</sup>

This patient's death might have been prevented had the diagnosis of mediastinal tumor been arrived at and surgical treatment instituted earlier. We agree with Lindskog and Kausel<sup>19</sup> that the indication for surgical excision of a presumptively benign mediastinal tumor rests on the demonstration of its existence.

#### CONCLUSION

A case of myocardial abscesses due to direct extension from a dermoid cyst is reported. The clinical, roentgenologic, electrocardiographic and pathologic findings are discussed. Earlier recognition and surgical removal might have prevented the fatal outcome.

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### CARCINOMA OF THE TAIL OF THE PANCREAS ASSOCIATED WITH BLEEDING GASTRIC VARICES AND HYPERSPLENISM\*

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UNFORTUNATELY, carcinoma arising in the body or tail of the pancreas seldom produces symptoms early enough so that it can be removed at operation. In many series in the literature, carcinoma of the body or tail of the pancreas was apparently quite unsuspected prior to operation or autopsy.<sup>1-4</sup> Even at operation, in the majority of instances, the local spread will be such that resection through uninvolved tissue will be impossible.<sup>1,2</sup> It is the purpose of this report to present an unusual case of carcinoma of the tail of the pancreas, manifested by massive melena, gastric varices and a peripheral blood picture compatible with the diagnosis of hypersplenism, in which surgical exploration led to the discovery of the tumor.

#### CASE REPORT

A 51 year old white male was admitted to Montefiore Hospital on February 19, 1951, with the chief complaint of melena of three months' duration. In December, 1950, the patient had been awakened from his sleep by a severe, sharp, piercing pain arising in his left lower anterior chest and left upper quadrant, which radiated posteriorly and was aggravated by breathing. This sharp pain persisted for four hours and then remained as a dull aching sensation in his left upper quadrant. On the morning of the following day, the patient passed the first of a succession of tarry stools. During the next two weeks he passed frequent tarry stools. By the end of this period, he had become extremely weak and had lost five pounds in weight.

On December 30, 1950, he was admitted to Polyclinic Hospital for therapy of his melena and anemia, with the diagnosis of bleeding peptic ulcer. The patient was placed on a Sippy régime, with coincidental cessation of his melena. He was discharged improved after a one week stay.

\* Received for publication June 20, 1951.

From the Medical and Surgical Services of Montefiore Hospital, New York, N. Y.

During the first week at home the patient remained asymptomatic. On the eighth day he passed a large, tarry, grossly bloody stool. After passing several similar stools he became prostrate and was re-admitted in shock to Polyclinic Hospital on January 16, 1951. He was promptly given 1 L. of blood and improved immediately. During the next four weeks his melena persisted, and 20 pints of blood were administered to combat blood loss. A gastrointestinal series, taken on February 12, was interpreted as demonstrating an esophageal hiatus hernia. Therapy consisted of a modified Sippy diet, ferrous sulfate and oral vitamin C and K administration. His melena ceased, and he was discharged on February 17 with the diagnosis of bleeding esophageal hiatus hernia. The patient had noted a 20 pound weight loss during his two Polyclinic Hospital admissions. On February 18 he suddenly developed a sharp pain in his left lower anterior chest and left upper quadrant which radiated into his back and was aggravated by breathing. A chill soon followed, accompanied by a temperature of 104° F. He was given sedation, penicillin and aureomycin, with prompt fall in his temperature to normal by morning. On the evening of February 19 he passed two grossly bloody black stools and was admitted to Montefiore Hospital.

The patient's past history was significant in two respects. First, 15 months before his present admission the patient had had a gastrointestinal series taken for symptoms of vague epigastric distress and flatulence not related to meals. This gastrointestinal series was interpreted as normal. Following this study, the patient's symptoms promptly disappeared without medical therapy. Second, because of a family history of diabetes mellitus, the patient had had his urine tested for sugar many times in the past 15 months, and on two occasions had been told he had a trace of sugar. Fasting blood sugars apparently were only slightly elevated, and the patient did not require any form of therapy for these findings.

At the time of entry, physical examination revealed the patient's temperature to be 99° F., pulse 100, respirations 22, and blood pressure 98/60 mm. of Hg. The patient appeared well nourished and quite apprehensive, but in no acute distress. His extremities were cool and moist. The mucous membranes were extremely pale. The fundi were normal. There was no evidence of jaundice or bleeding from the nose or mouth. No petechiae could be seen. No significant lymphadenopathy was present. Examination of the heart and lungs was negative. The abdomen was slightly distended and tympanitic. No fluid wave could be demonstrated. A firm, nontender spleen was palpated 5 cm. below the left costal margin. No other organs or masses were felt. Auscultation revealed active borborygmi. Rectal examination revealed a tarry stool, which was positive for blood. Neurologic examination revealed no abnormal findings.

The hematologic data were as follows: Blood count: red cells, 2,800,000; hemoglobin, 7.5 gm.; hematocrit, 22 per cent; white cells, 2,000; differential count: stab forms, 2 per cent; segmented forms, 58 per cent; lymphocytes, 28 per cent; eosinophils, 4 per cent; monocytes, 8 per cent. The erythrocytes were hypochromic, and platelets appeared diminished on smear; the platelet count was 92,400 and the reticulocyte count, 1.2 per cent. The bleeding time (Duke) was 3 minutes. Clotting time (capillary) was 3 minutes. The tourniquet test was weakly positive. Clot retraction was moderate after 6 hours. Prothrombin time was normal. Bone marrow aspiration revealed a hyperplastic marrow in which there was a marked increase in the erythroid elements. There was normal progression of maturation of both the erythroid and myeloid series. Slight eosinophilia was noted. Megakaryocytes were present in increased numbers, but many of them appeared to be deficient in platelet production. Urine examination was normal. Blood chemical findings were as follows: urea nitrogen, 23.4 mg. per cent; fasting sugar, 131 mg. per cent; cephalin flocculation, negative; thymol turbidity, 1 unit; total bilirubin, 1.3 mg. per cent; total protein, 5.9

gm. per cent; albumin, 4.5 gm. per cent; globulin, 1.4 gm. per cent; alkaline phosphatase, 2.6 Bodansky units; uric acid, 4 mg. per cent.

*Roentgenologic Findings:* Review of the gastrointestinal series taken at Polyclinic Hospital on February 12 revealed a normal esophagus, with no evidence of esophageal varices but some irregularity at the esophagogastric junction suggestive of



FIG. 1. Prone film one hour after the administration of the barium meal. Note the "bubble appearance" of the mucosal pattern in the fundal area of the stomach. Arrows point to a soft tissue shadow in the hilar area of the enlarged spleen.

hiatal insufficiency. An area of irregularity in the mucosal pattern of the cardia was also noted, but could not be adequately evaluated because of excess barium. The spleen appeared enlarged.

On February 28, repeat roentgen studies were made of the esophagus and upper gastrointestinal tract with special mucosal technic. A normal esophagus, without evidence of varices, was again demonstrated. The rugae in the fundal area of the stomach appeared thick and tortuous, and distortion of the mucosal pattern by clear areas was noted, giving this region a "bubble appearance" (figures 1 and 2). The diagnosis of fundal varices was considered, as well as the possibility of a gastric neoplasm. Considerable enlargement of the splenic shadow was also noted, with displacement of the lower two-thirds of the stomach toward the midline (figure 1).



FIG. 2. Oblique film taken in the prone position, clearly demonstrating the varices in the fundus and greater curvature of the stomach. Note the normal mucosal pattern of the esophagus.

An Einhorn string test, performed on February 19, clearly demonstrated a bleeding area 40 cm. from the teeth in the region of the cardiofundal area of the stomach. The tentative diagnosis was made of either splenic vein thrombosis with gastric varices or gastric carcinoma of the fundus. Therapy consisted of a Meulengracht diet and several blood transfusions. By the end of the first week gross melena had ceased and the hemoglobin had risen to 12.5 gm. There was also a slight rise in the white blood cell and platelet counts (figure 3). An exploratory laparotomy was performed on March 3.

*Operative Findings:* A left thoracoabdominal incision was made, removing the eighth rib. There were numerous large varicosities in the fundus of the stomach and

gastrosplenic ligament. The stomach was opened in the region of the fundus and a small ulcer was found on the anterior wall. In the base of this ulcer there was a large varicose vein from the surface of which fresh blood was oozing. No induration was noted around the ulcer.

The spleen was enlarged to about three times its normal size. Because of the preoperative diagnostic possibility of splenic vein thrombosis, the spleen was mobilized with the intent of investigating the splenic venous system. During this procedure a mass was palpated in the hilum of the spleen which, on visualization, measured about 1 inch in diameter. This appeared to be an intrinsic tumor of the tail of the pancreas, which had obstructed the venous system from the spleen. A splenectomy and resection of the pancreatic tumor were then performed. After a frozen section of the tumor revealed carcinoma of the tail of the pancreas, a hemipancrcreatectomy was done.

The incision in the fundus of the stomach was repaired. A drain was placed

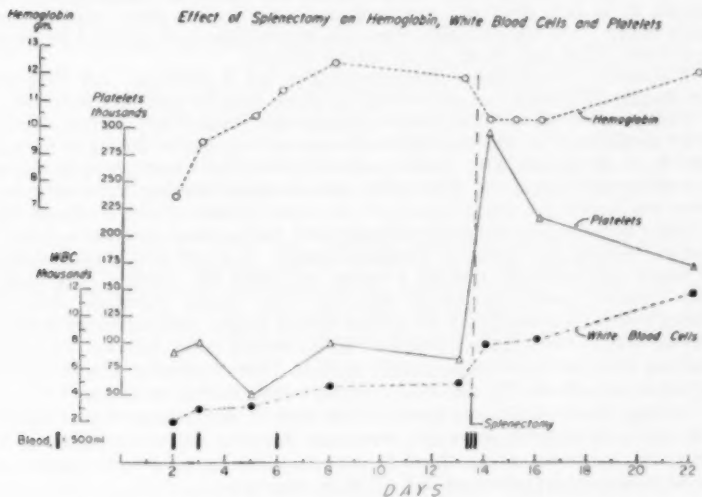


FIG. 3. Effects of transfusions and splenectomy on the blood counts.

adjacent to the stump of the pancreas and the wound closed in layers. Under-water drainage of the left chest cavity was instituted.

**Pathology Report: Gross Description:** The unfixed specimen included a spleen to which a portion of the tail of pancreas was densely adherent, and a separate portion of pancreas. The adherent portion of pancreas was an irregular tumor mass measuring 5.5 by 4 by 3 cm. It was separable from the spleen by blunt dissection. Its external surface was incompletely encapsulated, irregularly lobulated and tan-white in color. The surfaces of cut sections were firm, pink-white and studded with finely granular yellow-white foci. Approximately 4 cm. of the splenic vein and splenic artery remained attached to the spleen. Within 2 cm. from the hilum the splenic vein was completely surrounded by a protruding portion of the pancreatic tumor mass which compressed the lumen to a tiny slit through which a probe could not be inserted. The splenic artery was not remarkable. The separate portion of pancreas measured 4.5 by 3 by 1.5 cm. Approximately one-half of this was grossly normal pancreatic

tissue. The distal one-half, known to be contiguous with the previously described portion of the tail, also consisted of tumor tissue. The spleen measured 17 by 10 by 7 cm. and weighed approximately 400 gm. Its capsule was smooth and thin. Its cut surfaces were meaty in consistency and beefy red. The follicles and trabecular markings were obscure.

*Microscopic Description: Pancreas:* Sections from the tail consisted of an adenocarcinoma composed of irregular, varying sized acini lined by single layers of columnar cells containing scant cytoplasm and proportionately large ovoid nuclei within which atypical mitotic figures were apparent. The connective tissue stroma varied from loose areolar to dense collagenous in texture. The distal pancreatic ducts were irregularly dilated. Sections of pancreas from the vicinity of the proximal line of resection contained no tumor and were normal.

*Spleen:* The capsule and trabecular systems were not remarkable. Malpighian corpuscles were generally small and usually did not contain germinal centers. The sinusoids of the pulp stood out prominently and were lined by plump cells, but were usually empty. The intersinusoidal space was hypercellular and increased in amount, but was not stuffed with blood cells or notably fibrotic.

*Diagnosis:* (1) Anaplastic adenocarcinoma of tail of pancreas. (2) Congestive splenomegaly due to extrinsic compression of splenic veins by pancreatic carcinoma.

*Postoperative Course:* The patient's postoperative course was uneventful except for the development of persistent glycosuria and an elevation of fasting blood sugar values up to 200 mg. per cent. Platelet and white blood cell counts promptly returned to normal levels (figure 3). No further gastrointestinal bleeding occurred and the patient was discharged, greatly improved, two weeks postoperatively, on March 16.

After operation the patient was followed until death without recurrence of gastrointestinal bleeding, leukopenia or thrombocytopenia. A repeat gastrointestinal series one month postoperatively revealed a normal esophagus and stomach. His diabetic status remained moderately severe, requiring daily insulin injections. After his diabetes mellitus was controlled, the patient gained weight, returned to his usual occupation, and felt well for six months. Seven months postoperatively, the patient developed intestinal obstruction, diabetic acidosis, right ileofemoral thrombophlebitis and pulmonary emboli. He died after a stormy two week hospital course.

Autopsy revealed adenocarcinoma of the body of the pancreas with metastases to the liver, abdominal lymph nodes, mesentery, posterior wall of the stomach, duodenum and transverse colon. Thrombi were found in the pulmonary arteries, and several corresponding pulmonary infarcts were observed.

## DISCUSSION

The relation of gastrointestinal bleeding to pancreatic carcinoma of the body or tail of the pancreas has been emphasized in the work of Duff<sup>2</sup> and of Smalley and Eusterman.<sup>3</sup> There are three main causes for this bleeding. First, the stomach or intestine may be directly invaded by the pancreatic tumor or by peritoneal implants, with consequent ulceration and bleeding.<sup>3-7</sup> Second, obstruction of the portal circulation may lead to engorgement, dilatation and finally rupture of veins in the lower end of the esophagus, in the cardiofundal area of the stomach or in the rectum.<sup>8</sup> Third, impairment of blood coagulation mechanisms, resulting in a generalized hemorrhagic diathesis, may contribute to gastrointestinal bleeding. Prolonged jaundice with faulty absorption of vitamin K or diffuse metastatic involvement of the liver has been the explanation of these inhibitory effects on blood clotting.<sup>9</sup> In addition, the possibility of hypersplenism



due to obstruction of the venous drainage of the spleen, with subsequent congestive splenomegaly and thrombocytopenia, should be considered.

Splenomegaly in carcinoma of the body or tail of the pancreas is not uncommon; Duff noted this finding in 25 per cent of his cases.<sup>8</sup> The pathogenesis of this splenomegaly is most commonly due to obstruction of the portal circulation by invading tumor.<sup>8</sup> This is not unexpected if one recalls the intimate relationship of the pancreas to the portal and splenic veins, and remembers that the body and tail of the pancreas are drained by short venous channels into the splenic vein. Less frequently, the enlarged spleen may be due to actual invasion of the spleen by the tumor.<sup>3</sup>

The roentgen demonstration of gastric varices has been described by Templeton<sup>8</sup> and by Samuel.<sup>9</sup> They state that, in the development of esophageal varices, the gastric fundal veins become dilated before the lower esophageal plexus. Roentgen signs of gastric varices include the demonstration of thick tortuous mucosal folds over the greater curvature, extending up to the cardia, and the distortion of the mucosal pattern by the presence of round clear areas giving a "bubble appearance." Gastric varices are difficult to differentiate from gastric neoplasm on roentgen appearance. The coexistence of esophageal varices is significant, for both types of varices often exist together. If esophageal varices cannot be demonstrated, the differentiation from carcinoma becomes difficult. The presence of splenomegaly is more suggestive of gastric varices than of carcinoma.

In our case, the development of cardiofundal varices without the formation of esophageal varices depends on the following anatomic reasoning. The occlusion of the splenic vein at the hilum of the spleen forced the venous blood from this organ to go through the vasa brevia and veins located in the fundus of the stomach. The end result of the increased blood flow through these veins was the formation of dilated varicose veins in the cardiofundal areas of the stomach. The drainage of these vessels was back into the portal system via the left gastroepiploic and coronary veins rather than through the lower esophageal plexus into the left hemiazygous vein. Blakemore<sup>10</sup> has emphasized that obstruction of the flow of blood from the coronary vein into splenic or portal veins is an important factor in the formation of esophageal varices.<sup>11</sup> Apparently, in our case, the venous drainage of the stomach through the left gastroepiploic and coronary veins was sufficient to prevent the development of esophageal varices.

The syndrome of hypersplenism has become well established as a clinical entity in the past few years by Dameshek,<sup>12</sup> Doan,<sup>13</sup> Kracke<sup>14</sup> and others. A number of diseases of the spleen, both primary and secondary, have been found to produce this syndrome of splenomegaly associated with cytopenias, either total or selective.<sup>12-15</sup> Splenic vein obstruction, with resulting congestive splenomegaly, may be associated with depression of the cellular elements of the blood.<sup>15</sup> Carcinoma of the tail of the pancreas as the cause of this syndrome must be extremely rare, if one judges by the absence of reports in the literature.

#### SUMMARY

Attention is directed to a case of carcinoma of the tail of the pancreas which resulted in an unusual clinical picture, characterized by massive melena, a blood

picture compatible with the diagnosis of hypersplenism due to congestive splenomegaly, and the roentgen demonstration of gastric varices in the absence of esophageal varices.

Surgical exploration led to the discovery of the pancreatic tumor. An unsuccessful attempt was made to remove this tumor completely, and the patient died seven months postoperatively. Splenectomy, however, resulted in the correction of the blood picture and the disappearance of the gastric varices, with cessation of the gastrointestinal bleeding.

A discussion of possible mechanisms to explain the clinical findings in this case is presented.

#### ACKNOWLEDGMENT

We wish to acknowledge the aid given us by Dr. John Gruhn, of the Pathology Department of Montefiore Hospital.

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## MARKED LEUKOCYTOSIS RESULTING FROM CARCINOMATOSIS\*

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IN any patient showing a marked leukocytosis, leukemia is usually suspected first. However, leukocytosis of unusual degree may result from severe infection, intoxications, rapid blood loss or malignancy. This case is presented to illustrate that carcinoma of the suprarenal gland with widespread metastasis showing necrosis may result in a marked stimulation to the production of white blood cells.

### CASE REPORT

A 59 year old white female was admitted to St. Luke's Hospital on March 3, 1949. Her present illness had begun approximately eight weeks before admission with sudden onset of ease of fatigue, weakness and anorexia. The patient was confined to bed for the first three weeks and then began to get up occasionally, but she was so weak she had to return to bed. The last few weeks before admission the patient ran an afternoon fever up to 38.5° C. She was known to have lost 40 pounds since September, 1948.

The past history was significant in that the patient had had a carcinoma of the cervix diagnosed and treated with radium in 1942 in another hospital. There had been no vaginal bleeding since that time.

The physical examination revealed no abnormal physical findings other than inanition. On admission the red blood count was 2,920,000 and the hemoglobin 8.8 gm. The white blood count was 26,600, with a differential of 47 segments, 30 bands, 1 metamyelocyte, 5 eosinophils and 17 lymphocytes. Indices were: MCV 102, MCH 30, and MCHC 29 per cent. The platelet count was 230,000. A corrected sedimentation rate was 30 mm./hr., and the urinalysis was negative except for 1 to 2 white blood cells per high power field. Complete blood chemistry studies gave results within normal limits.

The day after admission the patient developed a fever of 39° C. This febrile course persisted for six and one-half weeks. Because of the possibility of septicemia, the patient was started on large doses of penicillin. The dosage was raised to 400,000  $\mu$  every two hours without affecting the elevated temperature. After a week of penicillin alone, other antibiotics were added in the usual adequate doses. The patient received courses of streptomycin and aureomycin without beneficial effect.

Extensive diagnostic studies were carried out. These included x-rays of the chest, skull and long bones, and pyelograms, all of which were considered normal. Agglutinations for typhoid, paratyphoid A and B, *Brucella suis* and *Br. melitensis* were negative. Repeated malarial smears and stool examinations were also negative. A total of nine blood cultures was done, none of which showed significant growth. The skin tests with tuberculin and histoplasmin were both negative. Repeated blood chemistry studies were all within normal limits.

The striking change in the laboratory findings during the patient's hospital stay was the steady increase in the white cell count. The peripheral blood showed a consistent differential of 80 to 85 per cent polymorphonuclear leukocytes, 30 to 50 per cent being band forms. During the month of April, the white blood cells rose from 39,850 to 80,000, with the same general differential count. Table 1 presents a summary of the leukocyte counts during the patient's hospital course.

\* Received for publication August 3, 1951.

The possibility of the patient's having leukemia was strongly considered. During the period of hospitalization three sternal punctures were done, none of which supported a diagnosis of leukemia. The patient's anemia became progressively severe, and repeated supportive blood transfusions were administered.

Numerous examinations revealed a mass in the left upper quadrant of the abdomen. Since all diagnostic studies were inconclusive, an exploratory laparotomy was done on April 20. At operation a large necrotic tumor was discovered retroperitoneally in the region of the upper pole of the left kidney. A biopsy was taken and the microscopic diagnosis was "retroperitoneal undifferentiated carcinoma."

The patient's condition deteriorated rapidly despite frequent blood transfusions. The white blood count rose steadily to 89,600, with the same high percentage of polymorphonuclear cells and band forms, and the patient died on June 3, 1949.

At autopsy a large necrotic tumor was found in the area of the left suprarenal gland, and this organ could not be identified. This tumor invaded, by direct extension, the upper pole of the left kidney, the left leaf of the diaphragm and the fundus of the stomach. The left main renal vein and the splenic vein were destroyed in the large

TABLE I  
White Blood Counts and Differential Counts during the Patient's Hospital Course

	WBC	Segs.	Bands	Meta.	Eos.	Lymphs.
March 1949						
10	26,600	47	30	1	5	17
19	32,800	54	33	0	1	9
29	36,000	47	30	3	8	10
April 1949						
7	41,800	49	33	3	9	4
14	62,800	47	35	1	9	7
20	81,000	41	48	2	6	3
May 1949						
6	59,400	48	45	0	5	2
16	61,600	69	25	0	3	2
25	88,000	51	44	4	0	1

tumor mass. Metastatic carcinoma was found in the liver, both lungs and the spleen, and in the wall of the right ventricle.

All of the metastatic nodules were characterized by large areas of necrosis. Microscopically, this tumor was composed of fairly large polyhedral cells with predominantly large and centrally located nuclei. The cytoplasm was light, with a foamy appearance. The final diagnosis was "undifferentiated carcinoma of the suprarenal gland."

#### DISCUSSION

The literature on the subject of leukocytosis in malignancy is not voluminous, but the subject is often discussed under the heading of the leukemoid reaction. By definition, this latter term implies the presence of sufficient numbers of immature leukocytes in peripheral blood to resemble a leukemia.<sup>1</sup>

One of the earliest reports was that of Shoemaker<sup>2</sup> in 1910, of a case of carcinoma of the stomach with a leukocytosis of 125,000. In 1926 Krumbhaar<sup>3</sup> reported 10 cases of varying clinical conditions showing the "leukemoid reaction." These included measles, pertussis, acute infection with lymphocytosis, acute in-

fection with hemorrhage, septicemia, mustard gas poisoning, multiple myeloma and a doubtful leukemia. The blood smear of many of these cases showed a marked cellular immaturity. Under the heading of acute infection with hemorrhage he described a patient with a bleeding, ulcerated carcinoma of the breast. In this patient the white blood cell count rose to 120,000, predominantly polymorphonuclear leukocytes and without blast cells.

Owens and Walker<sup>4</sup> reported a single case in 1934. Here an initial count of 28,700 was picked up in the preoperative workup for a herniorrhaphy. The patient returned several months later with symptoms referable to the stomach, and a carcinoma was found. The white blood cell count rose to 51,000 during this hospitalization, and cell immaturity was not described.

TABLE II  
Primary Cause of Leukocytosis of over 40,000 at St. Luke's Hospital  
during the Years 1946 to 1950

Year	Total Wbc's Done	Counts over 40,000	Primary Cause of Leukocytosis
1946	10,610	16	Infection 6
			Leukemia 6
			Hemolysis 1
			Necrosis of bowel 1
			Dehydration 1
			Acute pulmonary edema 1
1947	11,438	18	Infection 10
			Leukemia 6
			Hemolysis 2
1948	12,411	13	Infection 5
			Leukemia 3
			Acute hemorrhage 2
			Massive atelectasis 1
			Status asthmaticus 1
			Infectious mononucleosis 1
1949	14,181	16	Infection 5
			Leukemia 5
			Acute hemorrhage 1
			Dehydration 1
			Necrosis neoplasm 2
			Myocardial infarction 2

Meyer and Rotter<sup>5</sup> have reported two cases of carcinoma of the stomach in which the white blood cell count rose to 110,000 in one and 198,000 in the other. No blast forms were seen in the blood smears. In both of these cases the carcinoma had perforated and a secondary, localized peritonitis was shown at autopsy. Hinshaw and Hoxie<sup>6</sup> reported a case of carcinoma of the lung with a white blood cell count of 101,500, with 99 per cent mature polymorphonuclear cells.

It is apparent that most of the cases reported in this country have shown only marked leukocytosis without significant degrees of cellular immaturity. Sotelo-Ortiz,<sup>7</sup> however, has reported one case where a leukemoid reaction may have occurred. This patient developed carcinomatosis from a primary site in the ovary. The white blood cell count rose to 940,000, with 12 per cent myelo-

blasts. An autopsy was not done and, in view of this, it seems unfair to say definitely that this patient did not also have a leukemia.

The appearance of extreme leukocytosis is thus uncommon enough that it seemed appropriate to review the high white blood cell counts in our laboratory over a four year period to see if any similar cases appeared. A brief summary of this survey is presented in table 2. Two cases appeared in 1949. One of these is the case reported. Unfortunately, the other case could not be adequately studied. The diagnosis was melanosa, and the white blood cell counts ranged from 50,000 to 70,000 on just the few days that the patient was observed.

In all probability the extreme leukocytosis manifested by the patient reported in detail above was the result of the numerous and extensive areas of necrosis in the primary tumor and the metastases.

#### SUMMARY AND CONCLUSIONS

A case is reported which showed a marked leukocytosis in which the underlying disease was an undifferentiated carcinoma of the left suprarenal gland.

The pertinent literature is briefly reviewed.

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#### TREATMENT OF TEMPORAL ARTERITIS WITH CORTISONE: A CASE REPORT \*

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TEMPORAL arteritis, an uncommon disease affecting patients over the age of 55 years, and chiefly women, is characterized clinically by general manifestations including malaise, muscular and joint pains, anorexia, loss of weight, low grade fever, anemia, mild leukocytosis and increased sedimentation rate, and by local symptoms in the form of extremely painful, tender and thickened superficial temporal arteries. In one-third or more of cases there is a significant degree of

\* Received for publication January 2, 1952.

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visual impairment—in some instances bilateral total blindness—from involvement of the retinal arteries. The disease is self-limited, with an average duration of seven to eight months and a range of two to 30 months.<sup>1</sup> Pathologically it is a necrotizing, proliferative and granulomatous panarteritis affecting other portions of the arterial system as well as the superficial temporal arteries. The etiology is entirely unknown.

Ever since its initial recognition as a distinct clinical and pathologic entity in 1932 by Horton, Magath and Brown,<sup>2</sup> various therapeutic approaches have been attempted, among which iodides, arsenicals, sulfonamides, cobra venom, nicotinic acid, thiamine, mercury, liver and local irradiation may be listed as failures.<sup>1, 2, 3, 4, 5, 6, 7</sup> Local procaine infiltration along the temporal arteries has been reported to produce relief of local pain and tenderness.<sup>8</sup> One patient was relieved of pain by the use of the Sanders oscillating bed.<sup>9</sup>

It early became apparent that surgical resection of portions of the temporal arteries for purposes of biopsy resulted in striking relief of pain in most patients, and this is now an established method of treatment. The mechanism of pain relief is presumably section of periarterial nerve fibers. There are some instances in which fever and other general symptoms, as well as the local pain, have subsided after resection of portions of the temporal arteries. This has led to the suggestion that resection is of value as a prophylactic measure against retinal involvement, which, when it occurs, is a late manifestation, the implication being that the procedure actually affects the course of the disease.<sup>1</sup> Quite aside from the obvious theoretic objections to this interpretation, and apart from the self-limited nature of the disease, there are many cases on record in which this treatment had no effect on the general manifestations, and the number of such cases seems adequate to justify the conclusion that the procedure does not, in fact, affect the course of the disease.<sup>1, 4, 5, 10, 11, 12, 13, 14</sup> It is also true that resection of the temporal arteries has been known to be without effect even on the local symptoms,<sup>10, 12</sup> and to be followed by visual impairment months later.<sup>11, 13</sup>

More recently, good results in two patients treated with aureomycin have been reported by Rice-Oxley and Cooke, who conclude that further trial with this antibiotic is warranted.<sup>15</sup>

In 1950 Shick, Baggenstoss, Fuller and Polley reported briefly two patients with temporal arteritis of about four weeks' duration who were treated with cortisone.<sup>16</sup> Prompt relief of local and general symptoms resulted, with no recurrence during follow-up periods of 10 and 11 weeks. Ocular symptoms did not develop in either case. No other cases, to our knowledge, treated with cortisone or ACTH have been reported, and for this reason it was considered desirable that another case, treated apparently successfully with cortisone, be placed on record.

#### CASE REPORT

A 65 year old white woman was admitted to Albert Merritt Billings Hospital on April 11, 1951. She had been well until five weeks before, when she began to have generalized headache, mild initially, but gradually increasing in severity. Within one week after the onset, brief, severe, "stabbing" pains in the region of the temples appeared. About one week before admission she noted bilateral painful, tender swellings in the temples. The head pains were worse at night. Coincident with the onset of the headaches she became generally ill and weak, with loss of appetite and frequent nausea at mealtimes, and suffered from aching pain in the shoulders, elbows and knees,



increased by movement. In addition, she found it difficult to open her mouth wide to speak and masticate because of pain in the region of the temporomandibular joints. She had lost 15 pounds in weight. All her symptoms had increased steadily in severity since the onset. She had no visual disturbances.

On examination, the patient was an elderly woman who appeared ill and in great distress because of headache and lancinating pains in the temples. The skin and mucous membranes were rather pale, and her eyelids were puffy. Both superficial temporal arteries were greatly thickened, tortuous and extremely tender (figure 1). Pulsation was palpable in the affected vessels bilaterally. The overlying skin was edematous but not reddened. There were, in addition, several firm, tender nodules about 1 cm. in greatest dimension in the scalp of the occipital region in which pulsa-



Fig. 1. The patient as she appeared on admission to the hospital, with the characteristic tender, painful and visibly thickened temporal arteries.

tion was not palpable. The optic fundi were normal except for mild retinal arteriosclerosis, and the superficial peripheral arteries elsewhere were not exceptionally thickened. The peripheral pulses were normally palpable. Examination of the heart, lungs and abdomen was negative. There were no neurologic signs. Blood pressure was 136/86 mm. of Hg, and temperature was normal.

The red blood count was 3.98 million per cubic millimeter, the hemoglobin 11.9 gm. per cent, and the white blood count 11,600 per cubic millimeter, with 62 per cent polymorphonuclears, 34 per cent lymphocytes and 2 per cent eosinophils. The sedimentation rate was 55 mm. in one hour. The urine was normal. The blood Kahn reaction was negative. X-rays of the skull and chest were negative, and an electro-



FIG. 2. Low magnification of a section of temporal artery stained with hematoxylin and eosin, showing great thickening of intima and adventitia, cellular infiltration of media and adventitia, and necrosis of media.

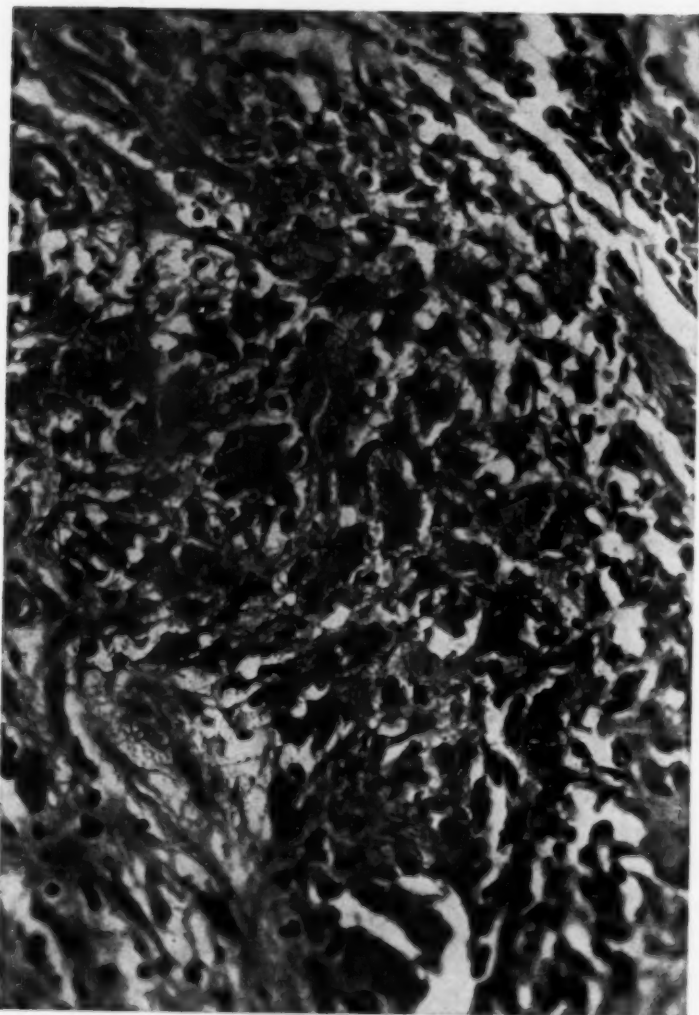


FIG. 3. High magnification of a portion of the media, showing multinucleated giant cells in a region of necrosis.

cardiogram was within normal limits. The spinal fluid was clear and colorless under normal pressure, and contained 2 lymphocytes per cubic millimeter, a total protein content of 32 mg. per cent; the Wassermann and colloidal gold reactions were negative.

A small segment of a branch of the left anterior superficial temporal artery, 0.7 cm. in length, was excised on April 18. Microscopic examination of this vessel revealed a greatly thickened intima with intact endothelium, patchy necrosis of the media with aggregations of multinucleate giant cells in the most affected portions, and lymphocytic infiltration in the adventitia and media (figures 2 and 3).

During the first week in the hospital the patient's symptoms remained unchanged. Morphine, codeine and salicylates had little effect on the pain. Her average daily caloric intake was no more than 650. She exhibited an irregular low grade fever, with peaks of 101.4° F. On April 19 treatment with cortisone was begun, in a dose of 100 mg. intramuscularly twice a day. On April 20 the headache and the local pain and tenderness in the temporal arteries were much less severe, and by April 23 had vanished. Her temperature curve fell immediately, and after April 23 she was afebrile. The malaise and general weakness also subsided rapidly, her appetite returned, and after April 24 she took about 2,000 calories in food daily. Between April 19 and May 1, when she was discharged from the hospital, she gained four pounds in weight. The thickening of the temporal arteries subsided more slowly. By May 8, however, when she was seen on an out-patient visit, there was no visible or palpable swelling remaining, nor were there any other subjective or objective signs of illness except for a sedimentation rate of 48 mm. in an hour. On May 17 this had fallen to 12 mm.

Treatment with cortisone was continued from April 19 until June 5. The dose was decreased from 200 mg. intramuscularly daily to 100 mg. on the third day of treatment, and further reduced to 50 mg. daily on the seventh day. After her discharge from the hospital on May 1, she took 50 mg. by mouth every second day until May 17, when the dose was reduced to 25 mg. every second day. Treatment was discontinued on June 5. When last heard from, on July 25, she reported no recurrence of symptoms.

#### SUMMARY

This report represents the third recorded instance known to the authors of temporal arteritis treated with cortisone. In the two previous cases and in this one the signs and symptoms, both local and general, subsided soon after treatment was begun, and no recurrence was noted after treatment was discontinued. Although the self-limited nature of the disease makes judgment of any therapy difficult, the duration of illness in each of the three patients treated with cortisone was significantly shorter than the average, which is seven to eight months.

#### ADDENDUM

Since this report was submitted for publication we have encountered reports of four cases of temporal arteritis treated successfully with ACTH,<sup>17, 18, 19</sup> and an additional case treated with cortisone.<sup>20</sup> In the latter, although both the local and the general symptoms responded quickly to cortisone, partial blindness developed in the left eye five days after treatment was begun. It is important to note, however, that the right eye had become affected to the point of complete blindness shortly before treatment was begun, and that the duration of symptoms at the time cortisone was started was approximately eight months. The possibility remains, therefore, that this failure to prevent ocular involvement was a result of the advanced stage of the disease at the time treatment was begun.

It is also of interest, in view of the favorable report by Rice-Oxley and Cooke<sup>18</sup> in regard to aureomycin, that this antibiotic was tried in two of the four cases treated later with ACTH, and found to be without effect.<sup>17, 19</sup>

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## EDITORIAL

### THE PROBLEMS OF TUBERCULOSIS CONTROL

RECENT advances in the treatment of tuberculosis have raised for new consideration the much debated question of proper balance among the various procedures employed in control of this disease. A review of past achievements, with an analysis of the current program, and a reevaluation of immediate objectives seem to be warranted at this time.

#### ACHIEVEMENTS OF THE LAST HALF CENTURY

For historical perspective in the problem it will be useful to review the accomplishments of the last fifty years in tuberculosis control by quarter centuries. The period from 1900 to 1925 was characterized by rapid advance in diagnosis through the development of roentgenological technics and improvement in bacteriological methods for detection of the tubercle bacillus. Treatment, which was essentially based on good hygiene and nutrition at the opening of the century, with emphasis on fresh air, proper food and rest, acquired, before the end of the quarter century, a specific character through the introduction of pneumothorax and surgical methods of collapse therapy.

The second quarter century was one of accelerated development of public health practice, with clear designation of specific elements in its operation, including case finding, hospitalization for purposes of isolation and care, a variety of measures for prevention, and finally social assistance for patients and their families with a view to prevention of economic disaster to the family and ensurance of working capacity for the patient in the future.

This brings us to the third quarter, which has just opened. Optimists, watching the declining curve of mortality from tuberculosis, predict a virtual eradication of the disease within this period in the United States and other countries with well developed programs. Conservatives see cause for concern in the continuing high prevalence of known cases, and propose either an intensification of present measures, or some revision of their character to lend new strength to the campaign. It has been pointed out by leaders in the Public Health Service that in any event there is immediate urgency in coördinating and integrating the practical measures in effect at present.<sup>1</sup>

Our decision as to the wisdom of a change in direction of effort or modification of emphasis on separate elements of the program will depend on our evaluation of the success of present measures. A brief summary of current practice and its results is presented herewith for consideration in that connection.

*Case Finding:* As practiced today, there are three major methods of case finding. The first and oldest is the discovery of cases by physicians in the

<sup>1</sup> Anderson, R. J., and Blomquist, E. T.: Tuberculosis control: a total program, *Public Health Reports* 66 (Tuberculosis Control Issue No. 59): 132, 1951.

private practice of medicine. Although private practitioners, as a class, devote little attention to the finer technics of tuberculosis control, they are the ones most likely to have first knowledge of cases that have reached the stage of actual symptoms.

The other two are, respectively, in the order of chronological development, search for cases on a contact basis, and mass roentgenographic survey of large segments of the population. The first of these is essentially clinic practice, by privately maintained or official dispensaries, and rests fundamentally on the recognized principle that one case of the disease comes from another. The second, or mass survey method, is the least personal of all three procedures; it is organized on the sound theory that a large enough, relatively inexpensive net will gather in most of the unknown cases that are sought.

*Medical Treatment:* As indicated above, medical treatment has improved enormously in the past fifty years, passing through the successive stages of primary emphasis on hygienic care, collapse therapy, surgical measures and drug treatment, to the present period of a well considered combination of chemotherapy and surgical practice, with stress on the need for effective long range rehabilitation. The cardinal requirement in the program is the hospital bed for tuberculosis, and it is indeed the crux of present day problems.

*Prevention:* Proper treatment in itself achieves a large part of an adequate program of prevention, because removal of sources of contagion from persons who might contract the disease is effected in the isolation ensured by proper hospital treatment. In the best organized communities in the country today hospital treatment of the patient is supplemented by supervision and education of his family at home in measures to avoid infection or detect it in time for arrest, if infection has already occurred. To this is added in small segments of our population, but in large segments in many communities abroad, BCG vaccination.

*Social Assistance:* This varies all the way from abolition of the means test as a requirement for hospital admission to direct financial grants to a patient's family to tide it over during the period of non-employment of the patient. An essential feature of all social assistance programs is physical and vocational rehabilitation of hospital patients, so that they may resume an economically independent position in society after recovery. All experience has shown a strong psychological element in this feature of the program, and the dependence of a patient's morale and faithfulness in taking treatment on the support given his family in his absence.

#### STATISTICS ON THE PROBLEM

The completion of the 1950 census, and the comparisons facilitated thereby on progress in tuberculosis control during the successive decades of the century, have prompted a series of useful analyses. Reference is made



to two summaries in particular, which are in general agreement, although varying slightly in details.<sup>2,3</sup>

*Mortality:* Tuberculosis mortality in the United States declined 90 per cent from 1900 to 1950. The pace of decline has actually accelerated within the last decade. The mortality in 1950 was only half that of 1945. Tentative figures indicate that the death rate for 1951 was 20 per 100,000 population. Gross figures for mortality furnish an inadequate picture of the total problem, however. A breakdown by race, sex and age shows that the mortality rate in non-white persons is at least three times that in white persons, that the death rate is twice as high in males as in females, and that, in contrast to the rates in the earlier years of the century, more than half of all deaths from tuberculosis now occur after the age of 45 years. Since whites greatly outnumber non-whites in the population, these figures mean, in brief, that the greatest number of deaths from tuberculosis today occurs in old white males. The steady attrition of the old tuberculous white males with advancing age is a significant factor in the general decline of tuberculosis mortality. Since for five decades the mortality curves for non-whites have tended steadily to approximate those for whites in character, in the light of the recognized currently increasing protection of youth, it seems probable that in a short time the highest total mortality will be seen in non-white males in the second half of life. Beyond that we need not try to forecast at the present time.

*Prevalence:* It is generally agreed that the *known* prevalence of the disease has declined little in the last twenty years. That improved case finding procedures and increased longevity of patients are partially responsible, is generally recognized. Official figures indicate that while the death rate has decreased rapidly and steadily, the known case rate has by no means kept parallel. With increase in the population, an actual rise in known cases may be anticipated in the future. The total number of cases of active disease in the United States, roughly calculated as 500,000 for many years, is now estimated, by agreement between the research staffs of the Public Health Service and National Tuberculosis Association, as 400,000, approximately 250,000 of which are known to health departments. About 90,000 of the total cases are believed to be sputum-positive.

*Incidence:* The average annual incidence of new cases reported in the whole country has been about 120,000 in recent years. The figure was 118,000 in 1951, a drop of some 19,000 cases from the peak of 137,000 in 1948. This drop is probably significant, since the case-finding measures in effect, which were in large measure responsible for a rise from about 117,000

<sup>2</sup> Case Finding, Tuberculosis Morbidity, and other Data, 1951. A Computation and Preliminary Analysis of Data Submitted by States on the Semi-Annual and Annual Tuberculosis Reports for the Calendar Year 1951. Circulated in mimeographed form by the Public Health Service, Federal Security Agency, Washington, D. C., 1952.

<sup>3</sup> Dempsey, Mary: Current status of the tuberculosis problem. Circulated in mimeographed form by the National Tuberculosis Association, New York, N. Y., 1952.

in 1942 to the peak in 1948, have been in full force or even accentuated in intensity in the most recent years.

*Hospitalization:* Hospitalization is recognized as the core of tuberculosis control. Responsible public health agencies have set up standards on the optimum number of beds, to be used for guidance in community planning. Until recently the minimum number of beds required for adequate control was judged to be two and a half times the number of deaths from tuberculosis annually in the community. Three beds per annual death were recommended. Many communities in this country are still far from meeting the minimum standard. Some, with as many as four, five or six beds per death, substantially exceed it. At present in the United States approximately 102,000 beds are set aside specifically for tuberculosis, 80 per cent of which are occupied. Some 24,000 in addition are available for tuberculous patients in mental and penal institutions. The National Tuberculosis Association<sup>2</sup> estimates that 50,000 more beds will be necessary to bring the provision of separate communities for the care of tuberculosis up to presently accepted standards. The standards themselves are in the course of change, however, and in the future may be based on known prevalence rather than deaths. It is not yet known how this will affect estimated bed requirements.

*Cost of Tuberculosis Program:* The annual total cost of tuberculosis control in the United States is calculated as \$350,000,000, exclusive of construction expense and the cost of training personnel.<sup>3</sup> This includes the sums spent on hospitalization, medical care, case finding, health education, rehabilitation, social assistance, medical research and pensions. By far the largest item is hospitalization, which is figured at an average of \$6.75 per patient per day, for a total of \$200,000,000 a year, or more than half the cost of the whole tuberculosis program. As a final figure we may note that, according to the same analysis, the average cost of one case of tuberculosis is about \$15,000.

#### COURSE FOR THE FUTURE

With this background we may now inquire as to the best plan for tuberculosis control in the future. Two courses are obviously open, viz., (1) to keep on as we are doing, taking advantage of every opportunity for improvement in present procedure, and (2) to revise the program by introduction of some new principle which will replace or supplement existing procedures.

With the past to guide us, we may rest reasonably well assured that in time the first of these procedures will accomplish its objective, i.e., the relegation of tuberculosis to a minor position among disease entities. This will be achieved only at great cost. It will mean a steady increase in measures for case finding, greater provision of hospital beds and larger sums for rehabilitation. In no one of these fields do experts feel that we have yet reached optimum performance. If monetary inflation continues, the dollar cost will magnify the increase. Even so, the price might be small in com-

parison with the misery and impoverishment entailed in allowing a grave preventable contagious disease to persist in our population.

A better course cannot be outlined with certainty at the present time. But some elements of the program should certainly be scrutinized with the utmost care before being fixed in our minds as final. First and foremost for such scrutiny is bound to be the hospital program, which costs \$200,000,000 at the present time and will probably cost more in the immediate future. The internist, with the financial magnitude of the problem before him, is likely to inquire if full advantage is being taken of the powerful force of private practice in supplementing hospital care. It is well known that, costly as it is, the hospitalization in effect does not provide for all the tuberculous patients who need institutional care. Throughout the country there are waiting lists for tuberculosis hospitals. This is in part at least the result of successful case finding programs. Once patients' failure to remain in hospitals was decried. Today the complaint is that new patients cannot be hospitalized because the incumbents of available beds should not, and as a matter of fact will not leave. They will not leave because their treatment is proving successful. The latest and best methods of surgery and chemotherapy have not as yet shortened the optimum period of hospital stay. Indeed they have frequently lengthened it, because patients are willing to remain for the maximum effectiveness of treatment.

Herein, however, lies one possibility for major change in which the private practitioner is concerned. May it not be that, after completion of the necessary elements of active therapy and the accompanying indoctrination in measures of personal care so well effected by our tuberculosis hospitals today, the time-consuming final steps in the cure, particularly the long continued chemotherapy lately recognized as essential, can be carried out at home, with safety and success, by private physicians?

In this suggestion there may be merit. Much depends on improvement in the understanding of tuberculosis by physicians in general practice. Even more depends on the character of the homes in which treatment is given. Tuberculosis is most prevalent today in the economically underprivileged, who live in substandard homes. As in so many cases in which medicine is intimately concerned, the problem is not purely medical, but is inextricably bound up with social issues. There is every reason to hope that the standard of living of that portion of the population now most subject to tuberculosis will continue to rise. But no part of the program can wait for completion of another part and in the meantime more intelligent application of the skills of practicing internists than has been made in the past may solve part of the problem. Competent home after-care of tuberculous patients who have reached a stage of safety for themselves and others after a satisfactory course of institutional treatment, is one possible way of saving hospital time and relieving bed shortages.

ESMOND R. LONG, F.A.C.P.

## REVIEWS

*Pharmacology in Clinical Practice.* By HARRY BECKMAN, M.D. 839 pages; 25 × 16.5 cm. W. B. Saunders Company, Philadelphia. 1952. Price, \$12.50.

The author of *Pharmacology in Clinical Practice* is well known to the medical fraternity by his classical book, *Treatment in General Practice*, which had a wide vogue for a period of two decades. Dr. Beckman for this period of time had been Professor of Pharmacology at Marquette University, and has embodied into this text the course which he has so adequately given to the many medical students at that school.

In general the present text reminds one very much of *Treatment in General Practice*. The author's same felicity of style is carried into this book. The style is informal, with many personal references. Tremendous emphasis is placed upon the individual disease and the specific treatment with the available pharmacologic agents.

The arrangement of the book is unique when compared with other text books in pharmacology. For example, the book is divided into two large sections. Section I consists of such sub-headings as Allergy, Anesthesiology, Antibiotics, Autonomic Pharmacology, Cardiology, Dentistry, etc. This section comprises the reading text of the book. Section II, on the other hand, is a compendium of drugs arranged in alphabetical order very much like one would find in Merck's Index or the United States Dispensatory. In Section I disease conditions are described briefly along with methods of treatment and rationale of the pharmacologic agent used. One misses in this section of the book the usual descriptions of mechanism of action based upon physiologic and biochemical processes. Rather the author has placed his emphasis upon the disease condition and its alleviation or cure by means of the pharmacologic agent. This will have a great appeal for many medical students; others will miss the basic theory underlying the mechanism of drug action.

The book appears to be as complete as is possible when one considers the inclusion of the ever-increasing list of pharmacologic agents. The typographical errors seem to be minimal and the format and style are appealing. It will be interesting to see whether this type of approach to the subject of pharmacology is that which is desired in the schools of medicine.

The book is a valuable addition to the library of the practitioner of medicine.

J. C. K.

*Joll's Diseases of the Thyroid Gland.* 2nd Ed. By FRANCIS F. RUNDLE, M.D., F.R.C.S. 520 pages; 24.5 × 18.5 cm. Grune and Stratton, Inc., New York. 1951. Price, \$12.75.

The first edition of this book appeared in 1932. Before Dr. Joll's untimely death in 1945, it was planned that the second edition should be revised and rewritten jointly with Dr. Rundle. Dr. Rundle has now tackled the job alone, with the exception of a few chapters contributed by colleagues, and the section on struma lymphomatosa written by Dr. Joll himself with little subsequent modification.

It is obvious that the two decades elapsing between the two editions have seen many and spectacular advances in the field of thyroid disease. Thus, while the mode of presentation and general scope of the first edition have been preserved, an abundance of new material has been added. Much of the new clinical matter has been taken directly from the author's Jacksonian prize essay.

After introductory chapters on histopathology, structure and development, simple goiter is comprehensively treated. The next section is devoted to hypothyroid states and is undesirably brief. One is surprised, among other omissions, to find no mention of Sheehan's syndrome among the mixed endocrinopathies that include hypothyroidism.

Thyrotoxicosis is then dealt with exhaustively, and much of the data on its ocular manifestations is based on the author's original work. Descriptions of developmental anomalies, acute inflammations, granulomatous diseases, struma lymphomatosa, Riedel's struma, subacute thyroiditis, malignant disease, hydatid disease and amyloid follow. Finally anesthetic and surgical technics are discussed in detail.

This text forms a readable, detailed and well illustrated treatise on the subject of thyroid disorders. An ample bibliography refers the reader widely and covers both the American and European literature. To the student of thyroid disease who requires a fairly comprehensive yet concise summary of the subject, this book can be recommended.

H. J. L. M.

*Diseases of the Heart and Circulation.* 2nd Ed. By ALBERT A. FITZGERALD PEEL, M.A., D.M. (Oxon.), F.R.F.P.S. (G), Physician for Diseases of the Heart, Victoria Infirmary, Glasgow. 472 pages; 14 × 22.5 cm. Oxford University Press, New York. 1952. Price, \$7.50.

This Scottish text is the fruit of the author's twenty years of teaching experience in Glasgow. It is based on Dr. Peel's lecture notes, and is therefore intended primarily as an introduction to cardiovascular disease for students and general practitioners.

Since the first edition in 1946 such procedures as auricular catheterization, phonocardiography, angiocardiology and electrocardiology with multiple unipolar chest leads have shed new light on many cardiovascular subjects, and this new knowledge is incorporated in the present edition. Among sections that have been rewritten are those dealing with abnormalities in the ventricular complexes of the cardiogram, with congenital heart disease, low blood pressure, gallop rhythm and the surgical treatment of hypertension. New sections on peripheral circulatory failure, pneumothorax, temporal arteritis, traumatic heart lesions, ballistocardiography and arterio-venous fistulae have been added.

The author intersperses the general orthodoxy of his text with a number of statements with which many authorities will not agree. He states that Dicumarol exerts a toxic action on the liver with resulting reduction in prothrombin formation; that an impalpable impulse with an average chest wall indicates emphysema, pericardial effusion or myxedema; that the normal third heart sound has been termed "the opening snap of the mitral valve"; that quinidine is absolutely contraindicated in patients with a history of previous embolism and also in auricular fibrillation complicating acute myocardial infarction. Other minor complaints are that he makes no mention of the use of radioactive iodine in the treatment of angina, that he subscribes to the theory of cerebral angiospasm to explain transient syndromes, and that he perpetuates the time-honored error that pulsus paradoxus is the reverse (rather than an exaggeration) of the normal.

The text as a whole is above serious criticism as an introduction to the subject of cardiovascular disease. It is simply and clearly written and its content is for the most part sound. There are, however, already a large number of excellent textbooks of cardiology readily available, and it is difficult to find a valid reason for singling this text out for special recommendation.

H. J. L. M.

*Manual of Electrocardiography.* By BENJAMIN F. SMITH, M.D., Professor of Clinical Medicine, Baylor University College of Medicine, Houston, Texas. 215 pages; 15.5 × 23.5 cm. Elsevier Press, Inc., Houston. 1952. Price, \$4.50.

The avowed purpose of this book is to start the undergraduate or practicing physician "... on the road to becoming an electrocardiographer, not a mere pattern recognizer." There are chapters on the usual electrocardiographic subjects, as well

as a 50 page section on the correlation of electrocardiographic and autopsy findings, and a short section on "Pen Pictures of Cardiology."

This book unfortunately fails to meet the purpose for which it was intended. Space devoted to the correlation of electrocardiographic and autopsy findings could have been better utilized to clarify many of the obscurities of the manual. The "Pen Pictures" are too brief and sketchy to be of real value to student or physician.

The reviewer can find little reason to recommend this manual in place of existing texts on electrocardiography.

L. S.

*The Unipolar Electrocardiogram: A Clinical Interpretation.* By JOSEPH M. BARKER, M.D., F.A.C.P., Cardiologist, Yater Clinic, and Associate Professor of Clinical Medicine, Georgetown University School of Medicine, Washington, D. C.; Assisted by JOSEPH J. WALLACE, M.D., F.A.C.P.; Advised by WALLACE M. YATER, M.D., F.A.C.P.; Foreword by FRANK N. WILSON, M.D., F.A.C.P. 660 pages; 17 x 25.5 cm. Appleton-Century-Crofts, Inc., New York. 1952. Price, \$12.50.

This book is intended to present "all the data necessary for the student and physician with little or no background in electrocardiography to gain the necessary working knowledge through persistence." The author emphasizes the need for a great deal of study and the absence of short cuts in acquiring such knowledge. Toward this goal he has assembled much information concerning electrocardiographic theory and practice. The theory is presented in great detail and with many diagrams and illustrations. Much of the text is in bold-face type. Reading is difficult because the discussions are too lengthy and involved and not sufficiently selective, because the diagrams are frequently not simple, and because of the too-generous use of bold-face sentences. The absence of directly indicated references to the bibliography detracts from the usefulness of this volume, especially where there is so much conjecture mingled with the facts. These criticisms are regrettable, for the content generally is good, and the approach usually sound.

S. S.

*Clinical Progress in Cardiovascular Disease—Modern Medical Monographs 2.* Edited by HERRMAN L. BLUMGART, M.D., Physician-in-Chief, Beth Israel Hospital, and Professor of Medicine, Harvard Medical School, Boston, Mass. 143 pages; 14 x 22.5 cm. Grune and Stratton, New York. Price, \$4.50.

This monograph consists of essays on five current problems in cardiovascular disease, which were originally published in the section on "Clinical Progress" of *Circulation* between March 1951 and February 1952. The symposium on arteriosclerosis is up to date and complete. There is an excellent critical appraisal of our knowledge of emotion and the circulation. Surgery for mitral stenosis is interestingly presented. The essays on the management of acute cardiac emergencies and on the care of cardiac patients in relation to surgery are adequate.

These are authoritative, up-to-date, critical reviews and discussions. The subjects are timely and of practical importance as well as theoretical interest to the internist. This small volume can be read with profit by the clinician.

S. S.

#### BOOKS RECEIVED

Books received during September are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Biologie d'Anopheles Gambiae: Recherches en Afrique-Occidentale Française.* World Health Organization Monograph Series No. 9. By M. H. HOLSTEIN, Dr. ès Sc.



176 pages; 24 × 16 cm. (paper-bound). 1952. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, \$2.00.

*Connective Tissues: Transactions of the Third Conference, February 14-15, 1952, New York, N. Y.* Edited by CHARLES RAGAN, Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, N. Y. 166 pages; 23.5 × 15.5 cm. 1952. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, \$3.50.

*Diabetic Glomerulosclerosis: The Specific Renal Disease of Diabetes Mellitus.* By HAROLD RIFKIN, M.D., F.A.C.P., Lecturer in Medicine, College of Physicians and Surgeons, Columbia University, etc.; LOUIS LEITER, M.D., Ph.D., Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University, etc.; and JAMES BERKMAN, M.D., Instructor in Pathology, College of Physicians and Surgeons, Columbia University, etc. 102 pages; 22.5 × 14.5 cm. (leather-bound). 1952. Charles C. Thomas, Publisher, Springfield, Illinois. Price, \$3.50.

*The Esophagus and Its Diseases.* By EDDY D. PALMER, M.D., F.A.C.P., Lieutenant Colonel, Medical Corps, United States Army; Chief, Gastrointestinal Section, Walter Reed Army Hospital, etc. 553 pages; 24.5 × 16 cm. 1952. Paul B. Hoeber, Inc., Medical Books Department of Harper & Brothers, New York. Price, \$15.00.

*Expert Committee on Insecticides: Third Report. World Health Organization Technical Report Series No. 46.* 36 pages; 24 × 16 cm. (paper-bound). 1952. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 25 cents.

*Expert Committee on Mental Health: Alcoholism Subcommittee, Second Report. World Health Organization Technical Report Series No. 48.* 39 pages; 24 × 16 cm. (paper-bound). 1952. World Health Organization, Geneva; available in U. S. A. through Columbia University Press, International Documents Service, New York. Price, 25 cents.

*Helping Parents Understand the Exceptional Child: "The Cornerstones of Understanding." Proceedings of the Annual Spring Conference on Education and the Exceptional Child, Under the Auspices of the Child Research Clinic of the Woods Schools at Langhorne, Pennsylvania.* 42 pages; 23 × 15 cm. (paper-bound). 1952. The Woods Schools, Langhorne, Pennsylvania. Price: Copies available on request to the Child Research Clinic, The Woods Schools, Langhorne, Pa.

*Malignant Disease and Its Treatment by Radium.* Volume IV. 2nd Ed. By SIR STANFORD CADE, K.B.E., C.B., F.R.C.S., M.R.C.P., F.F.R. (Hon.), Surgeon, Westminster Hospital, etc.; with a Foreword by SIR ERNEST ROCK CARLING, F.R.C.P., F.R.C.S., F.F.R., Consulting Surgeon and Vice-President, Westminster Hospital. 544 pages; 23.5 × 15.5 cm. 1952. The Williams and Wilkins Company, Baltimore. Price, \$12.50.

*Manual of Gynecology.* By E. STEWART TAYLOR, M.D., Professor and Head of the Department of Obstetrics and Gynecology, University of Colorado School of Medicine, Denver, Colorado. 204 pages; 24 × 15.5 cm. 1952. Lea & Febiger, Philadelphia. Price, \$4.50.

*Methods in Medical Research.* Volume 5. A. C. CORCORAN, Editor-in-Chief; "Methods for Separation of Complex Mixtures and Higher Molecular Weight" 176 pages; 24 × 16 cm. (paper-bound). 1952. World Health Organization,



CORAN, Editor; "Immunochemical Methods of Determining Homogeneity of Proteins and Polysaccharides," MELVIN COHN, Editor. Governing Board: IRVINE H. PAGE, Chairman; A. C. IVY, COLIN M. MACLEOD, CARL F. SCHMIDT, EUGENE A. STEAD, and DAVID L. THOMSON. 394 pages; 22.5 × 14.5 cm. 1952. The Year Book Publishers, Inc., Chicago. Price, \$7.50.

*Microbial Growth and Its Inhibition. First International Symposium on Chemical Microbiology. World Health Organization Monograph Series No. 10.* 285 pages; 24 × 16 cm. (paper-bound). 1952. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, \$3.00.

*Nerve Impulse: Transactions of the Third Conference, March 3 and 4, 1952, New York, New York.* Edited by H. HOUSTON MERRITT, M.D., Professor of Neurology, College of Physicians and Surgeons, Columbia University, New York, New York. 176 pages; 23.5 × 15.5 cm. 1952. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, \$3.50.

*Nutrition in the Practice of Medicine, with Comments on Nutrition, Disease and Geography: Proceedings of the Nutrition Symposium Held at the University of California, School of Medicine, San Francisco, October 30, 1951. Nutrition Symposium Series Number 4.* By J. ARNOLD BARGEN, PAUL R. CANNON, JOHN B. CONDLIFFE, PERRY J. CULVER, ROBERT M. KARK, HEINRICH NECHELES and FREDRICK J. STARE. 163 pages; 23 × 15.5 cm. (paper-bound). 1952. The National Vitamin Foundation, Incorporated, New York. Price, \$1.50.

*The Old Egyptian Medical Papyri: Logan Clendening Lectures on the History and Philosophy of Medicine, Second Series.* By CHAUNCEY D. LEAKE, Vice President, University of Texas—Medical Branch, Galveston. 108 pages; 21.5 × 14 cm. 1952. University of Kansas Press, Lawrence, Kansas. Price, \$2.00.

*Physician's Handbook.* 7th Ed. By MARCUS A. KRUPP, M.D., Assistant Clinical Professor of Medicine, Stanford University School of Medicine, etc.; NORMAN J. SWEET, M.D., Assistant Professor of Medicine, University of California School of Medicine, San Francisco; ERNEST JAWETZ, Ph.D., M.D., Associate Professor of Bacteriology and Lecturer in Medicine and Pediatrics, University of California School of Medicine, San Francisco; and CHARLES D. ARMSTRONG, M.D., Clinical Instructor in Medicine, Stanford University School of Medicine. 380 pages; 18 × 10.5 cm. 1952. Lange Medical Publications, University Medical Publishers, Los Altos, California. Price, \$2.50.

*Progress in Fundamental Medicine.* By PAUL CANNON, University of Chicago; J. A. CUNNINGHAM, University of Alabama; PAUL KLEMPERER, Mount Sinai Hospital, N. Y.; ALBERT KLIGMAN, University of Pennsylvania; G. K. MALLORY, The Mallory Institute; TRACY B. MALLORY (Deceased), The Massachusetts General Hospital; J. C. PATERSON, University of Western Ontario; L. B. STODDARD, University of Kansas; W. KENNETH CUYLER, Duke University; J. P. WYATT, St. Louis University; J. F. A. McMANUS (Editor), University of Virginia. 316 pages; 26 × 18 cm. 1952. Lea & Febiger, Philadelphia. Price, \$9.00.

*Research in Endocrinology.* By AUGUST A. WERNER, M.D., and Associates; edited by AL R. SCHMIDT, City Editor, Belleville Daily Advocate, Belleville, Illinois. 285 pages; 22 × 14.5 cm. 1952. The Von Hoffman Press; correspondence to be addressed to the author at 403 Humboldt Building, Saint Louis-3, Missouri. Price: 1,000 copies distributed free to medical libraries, medical publications and physicians.

- Rheumatic Fever: A Symposium Held at the University of Minnesota on November 29, 30, and December 1, 1951, under the Sponsorship of the Minnesota Heart Association.* Edited by LEWIS THOMAS, M.D. 349 pages; 24 × 15.5 cm. 1952. University of Minnesota Press, Minneapolis. Price, \$10.00.
- The Rockefeller Foundation: A Review for 1950 and 1951.* By CHESTER I. BARNARD, President of the Foundation. 125 pages; 23 × 15 cm. (paper-bound). 1952. The Rockefeller Foundation, New York. Available on request while supply lasts.
- A Stereoscopic Atlas of Human Anatomy. Section I: The Central Nervous System—in 4 volumes—with 34 View-Master Reels, and including a View-Master Stereoscope with light attachment and batteries.* By DAVID L. BASSETT, M.D., Associate Professor of Anatomy, Stanford University, California. Approximately 500 pages; 21.5 × 17.5 cm. (loose-leaf). 1952. Sawyer's Inc., Portland, Oregon.
- Viral and Rickettsial Infections of Man.* 2nd Ed. Edited by THOMAS M. RIVERS, M.D., Director of the Hospital, The Rockefeller Institute for Medical Research. 719 pages; 26 × 18 cm. 1952. J. B. Lippincott Company, Philadelphia. Price, \$7.50.
- The White Plague: Tuberculosis, Man and Society.* By RENE and JEAN DUBOS. 277 pages; 21.5 × 14.5 cm. 1952. Little, Brown and Company, Boston. Price, \$4.00.

## COLLEGE NEWS NOTES

### A.C.P. ANNUAL SESSION

The 34th Annual Session of the American College of Physicians will be held in Atlantic City, N. J., April 13-17, 1953. College headquarters will be at the Chalfonte-Haddon Hall Hotel, with the scientific program and technical exhibits being held in Convention Hall.

Immediately preceding the Annual Session, the American Heart Association will hold its yearly meeting, April 8-12, with headquarters at the Hotel Chelsea.

The Hotel Reservation Form used will accommodate members of both the American College of Physicians and the American Heart Association. A physician may, therefore, make reservations at the hotel of his choice for the entire period, if he desires to attend both meetings.

The complete program of the Annual Session of the College will be published in detail in the February issue of this journal.

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### A.C.P. ELECTION OF MEMBERS

The next meetings of the College Committee on Credentials at which action will be taken on proposals for membership will be held March 8 and April 11, 1953. Proposals must be in the Executive Offices sixty days in advance of the meetings of the Committee and should reach the College Governors at least ninety days in advance of these meetings.

Candidates elected to Associateship or advanced to Fellowship at the Committee meeting held earlier this month will be notified by their sponsors of the action taken, and a complete list of the elections will be published in the January issue of this journal.

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### A.C.P. POSTGRADUATE COURSES

At the time of preparation of this news item, Courses 1 and 2, RECENT TRENDS IN THE DIAGNOSIS AND TREATMENT OF CARDIOVASCULAR DISEASE, under Dr. Arthur M. Master, F.A.C.P., and Dr. Charles K. Friedberg, F.A.C.P., at Mount Sinai Hospital, and INTERNAL MEDICINE, under Dr. Roy R. Snowden, F.A.C.P., at the University of Pittsburgh School of Medicine, have been registered practically to capacity; in fact, Course No. 2 was considerably oversubscribed.

Three additional courses will have been concluded before the appearance of this news item; each had a satisfactory registration. They included a course in CARDIOVASCULAR DISEASE at Emory University School of Medicine, under Dr. R. Bruce Logue, F.A.C.P.; SELECTED TOPICS IN HEMATOLOGY at the New England Center Hospital, Boston, under Dr. William Dameshek, F.A.C.P., and a course entitled INTERNAL MEDICINE, CORRELATION OF NEW AND EXISTING BASIC AND CLINICAL FACTORS IN DIAGNOSIS AND TREATMENT at the Presbyterian Hospital, Chicago, under Dr. Frank B. Kelly, F.A.C.P.

The following courses are still to be given, and detailed outlines of the faculty personnel and of the daily presentations may be obtained through the Executive Secretary of the American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa.:

- No. 6. GASTRO-ENTEROLOGY: University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.; Dr. Henry L. Bockus, F.A.C.P., Director; Dec. 1-6, 1952.
- No. 7. INTERNAL MEDICINE: University of California School of Medicine, Medical Extension, at the Franklin Hospital, San Francisco, Calif.; Dr. Stacy R. Mettier, F.A.C.P., Director; Dr. H. Clare Shephardson, F.A.C.P., Co-Director; Dec. 8-12, 1952.
- No. 8. RECENT ADVANCES IN INTERNAL MEDICINE: University of Maryland and Johns Hopkins University Schools of Medicine, Baltimore, Md.; Dr. Maurice C. Pincoffs, M.A.C.P., and Dr. A. McGehee Harvey, F.A.C.P., Co-Directors; Dec. 8-12, 1952.

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#### A.C.P. REGIONAL MEETINGS

The North Dakota Regional Meeting was held at Grand Forks, September 13, 1952, under the Governorship of Dr. Robert B. Radl, and with Dr. C. H. A. Walton, College Governor for Manitoba and Saskatchewan, as the special guest. Papers were presented primarily by Associates of the College. Of the total of 21 members of the College in the State of North Dakota, 20 were in attendance. There were 18 non-member guests. Scheduled on the program was a showing of the Tele-Clinic Film of the 1952 Annual Session of the College at Cleveland, but unfortunately the film was lost in transit and did not arrive in time for showing. A Reception and Banquet were held at the Ryan Hotel in the evening, and it was addressed by Dr. Walton, whose subject was, "Your American College of Physicians."

The Western New York Regional Meeting of the College was held at Syracuse, N. Y., on Friday, October 3, 1952, under the Governorship of Dr. Edward C. Reifenstein, Sr., F.A.C.P. An exceptionally fine scientific program was given, which accounts largely for the unusually large attendance of around 200 physicians. Dr. T. Grier Miller, President of the College, gave a paper on, "The Care of the Patient with Ulcerative Colitis," and he, the Executive Secretary, Mr. E. R. Loveland, and Dean W. R. Willard, of the Medical College of Syracuse University, addressed the Banquet in the evening. Other special guests included Dr. Charles F. Moffatt, Montreal, Vice President of the College, and Dr. Karver L. Puestow, Madison, College Governor for Wisconsin.

The Western Pennsylvania Regional Meeting was held at Pittsburgh on Wednesday, October 8, 1952, under the Governorship of Dr. C. Howard Marcy, F.A.C.P., and the General Chairmanship of Dr. Roy R. Snowden, F.A.C.P. As a matter of fact, the program of this Regional Meeting formed an integral part of Postgraduate Course No. 2, INTERNAL MEDICINE, given for the College under the directorship of Dr. Snowden, October 6-11. There were some 63 physicians registered in the Course, and with a good representation of the members from Western Pennsylvania, the Regional Meeting was well attended. A Reception and Banquet were held at the Pittsburgh Athletic Association Annex in the evening and instead of having a Banquet program, the meeting adjourned to the Mellon Institute Auditorium, where the group listened to the Huggins Memorial Lecture, "Headache," by Dr. Harold G. Wolff, F.A.C.P., Professor of Medicine at Cornell University Medical College.

The Regional Meeting of the College for Montana and Wyoming was held at Great Falls, Mont., Friday and Saturday, October 10-11, 1952, under the Governorship of Dr. Harold W. Gregg, F.A.C.P. The Meeting opened on Friday evening with a Banquet at the Meadow Lark Country Club. Dr. Gregg was Toastmaster and Dr. Walter L. Palmer, F.A.C.P., Regent of the College and Professor of Medicine at the University of Chicago, was the guest speaker, his title being, "Internal Medi-

cine and the American College of Physicians." The scientific program was conducted on Saturday, October 11, at the Columbus Hospital, and the papers were given primarily by Associates and Fellows of the College, although there were a limited number of guests. A feature of the scientific program was a formal paper by Dr. Palmer on "The Present Status of Therapy in Peptic Ulcer" and a panel on "Ulcerative Colitis," over which Dr. J. A. Layne, F.A.C.P., presided as Moderator, and on which Dr. Walter L. Palmer, F.A.C.P., Dr. Robert McCleery, F.A.C.S., and Dr. Thomas F. Walker (Associate) were panel members.

The Pacific Northwest Regional Meeting was held this year at Vancouver, B. C., under the General Chairmanship of Dr. George A. Davidson, F.A.C.P., of Vancouver. The Meeting opened at 9 A.M. on Friday, October 17, at the Shaughnessy Hospital, and it was concluded by a session on Saturday morning, October 18. The territory covered the Provinces of Alberta and British Columbia and the States of Idaho, Oregon and Washington, the Governors of each territory cooperating in the preparation of the meeting. Speakers were selected from the various territories, and Dr. T. Grier Miller, President of the College, was the speaker at the Banquet on Friday evening at the Hotel Vancouver. Attendance records are not yet available, but it is assured that there was a large and enthusiastic participation of members and guests from the entire territory.

The Western Michigan Regional Meeting was held at Muskegon on October 22, 1952, and consisted of an evening program—presentation of cases: Diabetes by Dr. Jerome W. Conn, Ann Arbor; dinner, followed by a further presentation by Dr. Conn, "Modern Treatment of Diabetes."

The State of Oklahoma this year has not planned a formal Regional Meeting, but under the instigation of the Governor, Dr. Wann Langston, F.A.C.P., a get-together dinner was held in Oklahoma City during the meeting of the Oklahoma City Clinical Society, October 27, 1952.

The Arizona-New Mexico Regional Meeting was held October 29, 1952, at the United States Veterans Hospital Auditorium in Albuquerque, under the direction of Dr. Walter I. Werner, F.A.C.P., Governor for New Mexico. Dr. Ralph W. Mendelson, F.A.C.P., presided at the Scientific Session, which included the following presentations: "Modern Electrocardiography," Louis N. Katz, M.D., F.A.C.P., Chicago; "ACTH and Cortisone in Rheumatoid Arthritis," Charley J. Smyth, M.D., F.A.C.P., Denver; "Antibiotic Therapy," Gordon Meiklejohn (Associate), Denver; "Subacute Bacterial Endocarditis: Therapeutic Aspects," Eric P. Hausner, M.D. (by invitation), Santa Fe. A Reception and Banquet were held in the evening at the Albuquerque Country Club. Dr. Walter I. Werner, Governor, was the Toastmaster, and the address of the evening was delivered by Dr. Dwight L. Wilbur, F.A.C.P., San Francisco, Regent of the College.

The Seventh Regional Meeting of the College for the State of New Jersey was held at the Academy of Medicine of Northern New Jersey, Newark, Wednesday, November 5, 1952, under the Governorship of Dr. Edward C. Klein, Jr., F.A.C.P., and under the assistance of Dr. Asher Yaguda, F.A.C.P., as Chairman of Arrangements, and of Drs. Henry C. Crossfield, F.A.C.P., and Benjamin Saslow, F.A.C.P., Co-Chairmen of the Program Committee. The out of State speakers were William A. Jeffers, M.D., F.A.C.P., Assistant Professor of Clinical Medicine at University of Pennsylvania School of Medicine, Philadelphia, and Thomas H. McGavack, M.D., F.A.C.P., Professor of Clinical Medicine at the New York Medical College. Their subjects, respectively, were "Current Trends in the Treatment of Hypertension" and "Modern Concepts in the Diagnosis and Treatment of Thyroid Disease." A feature of the program was the showing of the Tele-Clinic Film of the Cleveland (1952) Annual Session of the College. The Reception and Dinner took place at the Downtown Club. Governor Klein presided and Dr. T. Grier Miller, President of the Col-

lege, was the special guest speaker. Among other special guests were George Morris Pierson, M.D., M.A.C.P., former Secretary General of the College, Philadelphia; George H. Lathrope, M.D., F.A.C.P., Regent of the College, Morristown; Thomas M. McMillan, M.D., F.A.C.P., Governor of the College for Eastern Pennsylvania, Philadelphia; Edward R. Loveland, Executive Secretary of the College, Philadelphia; Lemuel C. McGee, M.D., F.A.C.P., Governor of the College for Delaware, Wilmington; Irving S. Wright, M.D., F.A.C.P., Governor of the College for Eastern New York, New York City; Harrold A. Murray, M.D., F.A.C.P., President of the Medical Society of New Jersey, Newark; and, previously mentioned, Thomas H. McGavack, M.D., F.A.C.P., of the New York Medical College.

The Southeastern Regional Meeting of the College, embracing Alabama, Florida, Georgia, South Carolina and Cuba, was held at the University of Havana School of Medicine in Havana, November 7-8, under the Chairmanship of Dr. José J. Centurión, F.A.C.P., Governor for Cuba, and with the active participation of the Governors for the other states, Dr. Carter Smith, Georgia; Dr. E. Dice Lineberry, Alabama; Dr. William C. Blake, Florida; and Dr. Robert Wilson, Jr., South Carolina. The Committee on Scientific Program consisted, for the United States, of Drs. Carter Smith, Atlanta, Harry Harper, Augusta, D. O. Wright, Birmingham, Robert Wilson, Jr., Charleston, and Jack O. Rash, Miami; and, for Cuba, of Dr. Angel Vieta, Havana, Dr. Felix Hurtado, Havana, and Dr. J. Manuel Viamonte, Sr., Havana. This was the first occasion any formal College Meeting has been held in Cuba, and the meeting was arranged just prior to the Annual Session of the Southern Medical Association in Miami, November 10-14, with the thought that many of our Southern members could take advantage also of the Havana program. Speakers on the program included members from the various states and both members and non-members from Cuba. Dr. Edward L. Bortz, F.A.C.P., a Regent of the College, Philadelphia, gave a paper on "Prophylactic Geriatrics." Other special guests included Dr. T. Grier Miller, President of the College, and Mr. E. R. Loveland, Executive Secretary of the College, both of Philadelphia. An extensive program of entertainment both for the men and their wives was provided. On Friday evening a Reception and Banquet were held at the Vedado Tennis Club, with Dr. Carter Smith acting as Toastmaster and Dr. Centurión giving the principal address, "The American College of Physicians in Cuba." Responses were added by Dr. T. Grier Miller, President of the College, Mr. E. R. Loveland, Executive Secretary, and by Dr. Edward L. Bortz, Regent of the College.

The Midwest Regional Meeting, embracing the States of Illinois, Indiana, Iowa, Michigan, Minnesota, Ohio and Wisconsin, was held at Chicago on November 22, 1952. Dr. Howard Wakefield, F.A.C.P., College Governor for Northern Illinois, was General Chairman, but each of the Governors of the other States participated in the preparation of the program. Furthermore, each of the participating Governors presided at some particular session on the program. This program is probably the most intensive one on record; 24 separate presentations were made by 62 authors. Each presentation was limited to 15 minutes and the program was kept strictly to schedule. In the evening a social hour and Banquet were given in the Gold Room of the Congress Hotel, and Dr. Wakefield was the Toastmaster. There were numerous distinguished guests including President T. Grier Miller, Philadelphia, Executive Secretary E. R. Loveland, Philadelphia, Dr. J. Roscoe Miller, F.A.C.P., President of Northwestern University, Dr. Ernest E. Irons, M.A.C.P., Past President of the College, Dr. William S. Middleton, M.A.C.P., Past President of the College, Dr. Walter L. Palmer, F.A.C.P., Regent of the College, Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Regent of the College, Dr. A. B. Brower, F.A.C.P., Dayton, Regent of the College, Dr. M. A. Blankenhorn, F.A.C.P., Cincinnati, Regent of the College, Dr. George F. Lull, F.A.C.P., Secretary and General Manager of the American



Medical Association, General Paul R. Hawley, F.A.C.P., Director of the American College of Surgeons, Dr. Edwin L. Crosby, Director of the Joint Commission on Accreditation of Hospitals, and Mr. George Bugbee, Executive Director of the American Hospital Association. There was an exceptional program of entertainment, both at the Banquet and for the ladies during the day. Dr. Fred E. Ball, F.A.C.P., was the Treasurer for the Meeting and was in charge of the arrangements for the Luncheon and Banquet.

Coming Regional Meetings already scheduled include the following:

KENTUCKY at Lexington, November 29, 1952.

NORTH CAROLINA at Winston-Salem, December 4, 1952.

EASTERN PENNSYLVANIA at Philadelphia, January 16, 1953.

COLORADO at Denver, February 17, 1953.

VIRGINIA, probably at Norfolk, February 26, 1953.

DELAWARE at Wilmington, February 27, 1953.

KANSAS at Kansas City, March 20, 1953.

NORTH DAKOTA at Fargo, September 12, 1953.

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#### BINDING THE ANNALS OF INTERNAL MEDICINE

Frequent inquiries are sent to the Executive Offices of the College concerning binding the *Annals of Internal Medicine*. The College does not itself take orders for binding the *Annals*, although it does receive orders for Volume Box Files. These Volume Files are regularly advertised in this journal. The Volume Files are a satisfactory filing medium, but, of course, the various copies of the journal are not fastened in and may be taken out and lost or misplaced by the user. Those who want permanent file bindings with an index of the volume placed in the front thereof may obtain reliable and economical service from the Publishers' Authorized Binding Service, 308 W. Randolph St., Chicago 6, Ill. The College has carefully investigated their work, service and prices, and can recommend this company. Their current charge for binding a volume of the *Annals of Internal Medicine* is \$3.15, which includes the return postage charges.

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#### A.C.P. MEMBERS IN THE FAR EAST

The following members of the American College of Physicians presently are in the Far East:

Col. Charles L. Leedham (MC), USA, F.A.C.P., Consultant, Internal Medicine, Medical Section, Far East Command; Col. Walter M. Bartlett (MC), USA, F.A.C.P., Deputy Surgeon, Korean Communications Zone; Col. Clifford A. Best, Sr. (MC), USA, F.A.C.P., Commanding Officer, 14th Field Hospital; Col. George M. Powell (MC), USA, F.A.C.P., Chief, Medical Service, Osaka Army Hospital; Col. Ryle A. Radke, Sr., (MC), USA, F.A.C.P., Chief, Medical Service, Tokyo Army Hospital; Col. Donald B. Peterson (MC), USA (Associate), Consultant in Psychiatry, Medical Section, Headquarters, Far East Command; Col. John H. Taber (MC), USA (Associate), Commanding Officer, Army Hospital, Fukuoka; Col. Roy F. Roberts (MC), USA (Associate), Medical Consultant, Headquarters, Eighth Army.

Among those who have recently left the Far East Command for the United States are Col. Kenneth A. Brewer (MC), USA, F.A.C.P. (Valley Forge Army Hospital, Phoenixville, Pa.); Col. Edward A. Cleve (MC), USA (Associate) (Letterman Army Hospital, San Francisco, Calif.); Col. August A. Hall (MC), USA, F.A.C.P. (Edgewood Arsenal, Md.); Col. Charles J. Hornisher (MC), USA (Associate) (Camp Pickett, Va.); Col. Tyron E. Huber (MC), USA (Associate) (Army Graduate



School, Walter Reed Army Medical Center, Washington, D. C.); Col. Francis W. Pruitt (MC), USA, F.A.C.P. (Letterman Army Hospital, San Francisco, Calif.); Col. John T. B. Strode (MC), USA (Associate) (Camp Gordon, Augusta, Ga.); Col. Thomas A. Haedicke (MC), USA (Associate), and Lt. Col. Carroll S. Svare (MC), USA (Associate).

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#### TULANE UNIVERSITY OFFERS POSTGRADUATE COURSES

Tulane University of Louisiana School of Medicine, Division of Graduate Medicine, 1430 Tulane Avenue, New Orleans 12, La., has announced the following Postgraduate Courses:

Electrocardiography: George E. Burch, M.D., F.A.C.P., Chairman; December 1-12, 1952.

Pediatrics for Specialists: Dr. R. V. Platou, Chairman; February 23-28, 1953. Seminar on Low Back Pain: Dr. Jack Wickstrom, Chairman; February 27-28, 1953.

Internal Medicine in General Practice: Dr. J. Robert Snavelly and Dr. George E. Burch, F.A.C.P., Chairmen; March 23-27, 1953.

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#### INTERNATIONAL ACADEMY OF PROCTOLOGY OFFERS AWARD

The International Academy of Proctology, 43-55 Kissena Blvd., Flushing 55, N. Y., has announced an annual cash prize of \$100 and Certificate of Merit for 1952-53 for the best unpublished contributions on proctology or allied subjects. Competition is open to all physicians in all countries. Winning contributions will be selected by a board of impartial judges. The formal award and the presentation of certificates will be made at the annual convention of the Academy during May, 1953. Entries will be limited to 5,000 words, must be typewritten in English and submitted in five copies. Entries must be received by the Academy not later than April 1, 1953.

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#### UNIVERSITY OF PENNSYLVANIA ANNOUNCES APPOINTMENT OF NEW VICE PRESIDENT IN CHARGE OF MEDICAL AFFAIRS

The University of Pennsylvania through President Harold E. Stassen has announced the appointment of Dr. Norman H. Topping as Vice President in Charge of Medical Affairs, effective November 1, 1952. Dr. Topping has been Associate Director of the National Institutes of Health at Bethesda, Md., the research branch of the Public Health Service. He has also served as Assistant Surgeon General of the Public Health Service. Dr. Topping graduated in medicine from the University of Southern California School of Medicine in 1936, whereupon he was commissioned in the Public Health Service and served as an interne in its hospitals at San Francisco and Seattle. After a brief tour of duty he was assigned to research work at the National Institutes of Health in 1937. During World War II he was a Consultant to the Army as a member of the U. S. Typhus Commission, a work that earned him the Typhus Commission Medal. From 1946 to 1948 he was Assistant Chief of the National Institutes of Health, Division of Infectious Diseases; in 1948 he was appointed Associate Director and Assistant Surgeon General of the Public Health Service. Since then he has devoted most of his time to the administration of the National Institutes of Health's broad program of scientific research in heart disease, cancer, metabolic and neurological diseases and other afflictions of man.

Dr. Topping is a member of the Association of American Physicians, American Public Health Association, American Academy of Tropical Medicine, American Epidemiological Society, the Society of Experimental Biology and Medicine, and others.

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TRIBUTE PAID TO DR. POTTENGER

For some years it has been the custom of former patients and professional friends to forgather on the grounds of the Pottenger Sanatorium and Clinic at Monrovia, Calif., to do honor to Dr. Francis M. Pottenger, Sr. On September 21, 1952, several hundred of his former patients, admirers and friends held the annual "home-coming" celebration at the Sanatorium, just prior to his 83rd birthday on September 27. Dr. Pottenger, from the beginning of his early career, after the death of his young wife from tuberculosis, has devoted his whole time to the fight against that disease. Dr. Pottenger first began work on tuberculosis at Monrovia when the annual toll from tuberculosis was 200 out of every 100,000. It has now been reduced to 20 per 100,000. At the "home-coming" there was present one patient who left the Sanatorium in 1904, who has been working steadily and fulfilling his place in life. There are at least six patients who were at the Sanatorium in 1904 who are still living useful lives. Both of Dr. Pottenger's sons are physicians, Dr. Francis M. Pottenger, Jr., F.A.C.P., and Dr. Robert T. Pottenger.

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Dr. S. Spafford Ackerly, F.A.C.P., was presented with an outboard motor and with a silver tray inscribed "for twenty years of unselfishly dedicated service to his friends, profession, students, university, city, and state." The presentations were made at a recent party given for him by former students, psychiatrists, social workers and others interested in mental hygiene. Dr. Ackerly is Head of the Department of Psychiatry at the University of Louisville School of Medicine, and is Medical Director of the Louisville Mental Hygiene Clinic.

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Dr. Thomas A. Pitts, F.A.C.P., Columbia, S. C., has been awarded the medal of the American Cancer Society for his exceptional service to the 1951 cancer program.

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Dr. William Cabell Moore, F.A.C.P., Washington, D. C., received a certificate for meritorious service from the Medical Society of the District of Columbia during its annual scientific assembly. Under the presidency of Dr. Wallace M. Yater, F.A.C.P., the Society convened in Washington Sept. 29-Oct. 1.

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Capt. John R. Poppen (MC), USN (Retired), F.A.C.P., Drexel Hill, Pa., recently received the John Jeffries Award of the Institute of Aeronautical Sciences. Capt. Poppen, who retired last June as Director of the Naval Aviation Medical Acceleration Laboratory in Johnsville, Pa., is the second Navy medical officer to be so honored.

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Dr. Stanley William Olson, F.A.C.P., former Professor of Medicine and Dean of the University of Illinois College of Medicine, has recently been appointed Dean of the Baylor University College of Medicine, Houston. Dr. Olson, who is 38 years old, received his education at the University of Wisconsin, Wheaton College, University of Illinois College of Medicine and the University of Minnesota. He undertook postgraduate studies at the University of Minnesota and the Mayo Foundation, where he was Assistant Director for three years until he accepted the Illinois post in 1950.

Dr. R. Lee Foster (Associate), Phoenix, has been elected Secretary-Treasurer of the Arizona Radiological Society.

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Dr. Charles H. McEnerney, F.A.C.P., has been elected President of the Rheumatism Society of the District of Columbia.

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A past president of the West Virginia State Medical Association, Dr. Frank J. Holroyd, F.A.C.P., Princeton, has recently been appointed a member of the state Medical Licensing Board, his term ending June 30, 1957.

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Dr. Walter A. Bloedorn, F.A.C.P., Dean of George Washington University School of Medicine, Washington, D. C., has been appointed to a six-year term on the National Board of Medical Examiners.

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Dr. Perry F. Prather, F.A.C.P., Hagerstown, has recently been made Deputy Director of the Maryland State Department of Health. Dr. Prather had been Director of the Hagerstown and Washington County Department of Health.

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Dr. Samuel Benjamin, F.A.C.P., and Dr. Lawrence J. Thomas, F.A.C.P., have been elected President and Second Vice President, respectively, of the Diabetic Association of the District of Columbia.

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Dr. W. C. Davison, F.A.C.P., Dean of Duke University School of Medicine, Durham, has been appointed to the new Advisory Group of the Armed Forces Medical Library. The Group, composed of four other civilians and four officers of the Armed Forces, replaces the Association of Consultants to the Army Medical Library. Dr. Davison was formerly President of the Association and Chairman of the Executive Committee.

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Dr. Kenneth D. A. Allen, F.A.C.P., Denver; Dr. Lester R. Dragstedt, F.A.C.P., Chicago, and Dr. Laurentius O. Underdahl (Associate), Rochester, Minn., were three of the out-of-state speakers at the annual meeting of the Montana Medical Association, held in Missoula, Sept. 18-21. The panels on internal medicine and radiology, in which Dr. Underdahl and Dr. Allen participated, were sponsored by the Montana-Wyoming region of the College.

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Dr. Louis H. Bauer, F.A.C.P., Hempstead, N. Y., who was one of the guest speakers at the banquet, discussed "Medicine, the Public and Citizenship."

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Dr. Garfield G. Duncan, F.A.C.P., Philadelphia, and Dr. Roland P. Mackay, F.A.C.P., Chicago, were two of the guest speakers of the Michigan State Medical Society, when the Society met for its annual session in Detroit, Sept. 24-26. At the meeting of the Michigan Allergy Society, held in conjunction with the State Society meeting, Dr. Samuel M. Feinberg, F.A.C.P., Chicago, delivered an address.

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Dr. Tinsley R. Harrison, F.A.C.P., Birmingham, Ala., and Dr. Don W. Chapman, F.A.C.P., Houston, were the guest speakers at the Postgraduate Conference in Cardiology, sponsored by the Dallas Southern Clinical Society in September. In addition to acting as moderators in panel discussions, Dr. Harrison spoke on "The Kineto-cardiogram: A Study of Precordial Forces" and on "The Reproduction of Cardiovascular Symptoms," and Dr. Chapman used as his topics "Use of Cardiac Catheteriza-

tion in the Diagnosis of Congenital Heart Disease" and "Clinical Selection of Patients of Mitral Valvulotomy Including Cardiac Catheterization Studies."

Dr. J. Lamar Callaway, F.A.C.P., Durham, N. C., participated in symposia and spoke on "Pyogenic Dermatoses, Their Treatment and Complications" and "The Current Status of ACTH and Cortisone in Dermatologic Therapy" at the Postgraduate Conference in Pediatrics and Pediatric Dermatology, also sponsored by the Dallas Society.

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Dr. Franklin David Murphy, F.A.C.P., Chancellor of the University of Kansas, Kansas City, Kans., delivered the Convocation Address at the 25th anniversary of the opening of the hospitals and clinical departments of the University of Chicago School of Medicine. Dr. Lowell T. Coggeshall, F.A.C.P., Dean of the Division of Biological Sciences, University of Chicago, presided at a symposium on the progress of medical science, held as part of the anniversary proceedings, Oct. 4-5. Dr. William S. Middleton, M.A.C.P., Madison, Wis., presented a paper entitled "The Advance of Clinical Investigation," and Dr. Leonard A. Scheele, F.A.C.P., The Surgeon General, U. S. Public Health Service, delivered a paper on "Clinical Investigation in the Field of Public Health." As part of the scientific program at Billings Hospital, Dr. Richard V. Ebert, F.A.C.P., Minneapolis, spoke on "Studies on the Pathologic Physiology of Pulmonary Emphysema" and Dr. Arthur J. Vorwald, F.A.C.P., Saranac Lake, discussed "Clinical and Experimental Pneumonoconioses."

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Dr. Louis H. Bauer, F.A.C.P., Hempstead, N. Y., using as his topic "Medical Societies, The Doctors and The Public," addressed the annual combined meeting of the New Hampshire and Vermont state medical societies, held in Bretton Woods, N. H., in September. Dr. Herrman L. Blumgart, F.A.C.P., Boston, was also one of the guest speakers.

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At the Fifth Annual Session of the Nashville Medical Assembly, held Oct. 29-31 in Nashville, Tenn., Dr. William D. Robinson, F.A.C.P., Ann Arbor, spoke on "Management of Rheumatoid State"; Dr. Richard B. Capps, F.A.C.P., Chicago, on "Diagnosis and Management of Diseases of the Liver," and Dr. A. Carlton Ernstone, F.A.C.P., Cleveland, on "Management of Congestive Failure."

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At the One Hundred Second Annual Session of the Medical Society of the State of Pennsylvania, held in Philadelphia, Sept. 29-Oct. 3, Dr. Elliott P. Joslin, M.A.C.P., Boston, presented a paper entitled "Diabetic Coma." Other guest speakers and their topics included: Dr. Chester S. Keefer, Boston, A.C.P. Governor for Massachusetts—"Antibiotics Yesterday and Today"; Dr. E. Perry McCullagh, F.A.C.P., Cleveland—"Recent Advances in Endocrinology"; Abraham H. Aaron, F.A.C.P., Buffalo, N. Y.—"Intractable Peptic Ulcer"; Dr. Alvan L. Barach, F.A.C.P., New York City—"Newer Concepts on the Management of Emphysema"; Dr. Robert D. Taylor, F.A.C.P., Cleveland—"Medical Management of Hypertension," and Dr. Edgar A. Hines, Jr., F.A.C.P., Rochester, Minn.—"Medical Treatment of Occlusive Arterial Diseases." Dr. Walter F. Donaldson, F.A.C.P., Pittsburgh, was the Guest of Honor at the Fifth Annual State dinner held on Monday.

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Dr. Wallace W. Lindahl, F.A.C.P., Dr. John K. Martin, F.A.C.P., and Dr. William E. Watts (Associate), all of Seattle, were among those who presented papers at the fall meeting of the North Pacific Society of Internal Medicine, which met in

Sun Valley, Idaho, Sept. 19-20. Their respective topics were "Multiple Sclerosis," "Case Report of Waterhouse-Friderichsen Syndrome," and "Exophthalmus of Exophthalmic Goiter—A Case."

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Dr. John H. Lamb, Jr., F.A.C.P., Oklahoma City, was one of the guest speakers at the annual Southwest Regional Cancer Conference, which took place in Fort Worth, Tex., Sept. 24-25.

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Dr. Edgar Mayer, F.A.C.P., New York City, using as his topic "Treatment of Inoperable Cancer of the Lung," addressed the annual meeting of the Wisconsin Chapter of the American College of Chest Physicians, when the society met in Milwaukee, Oct. 5.

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Dr. Burrill B. Crohn, F.A.C.P., New York, discussed "Early Diagnosis of Gastric Malignancy" at a joint meeting of the Chicago Medical Society and the Postgraduate Course in Diseases of the Gastrointestinal Tract, Liver, and Pancreas. The meeting was held in Chicago on Oct. 8.

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Dr. Paul Dudley White, F.A.C.P., Boston, presented "Our Ignorance About Heart Disease in Days Gone By" at a meeting of the North Side Branch of the Chicago Medical Society when the Society convened in a joint meeting Oct. 2 with the physicians attending the first postgraduate course on cardiovascular and renal diseases sponsored by the Chicago Medical Society.

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At the Daniel Drake Memorial Meeting, the name of this year's meeting of the Kentucky State Medical Association, Dr. Richard B. Capps, F.A.C.P., Chicago, spoke on "Infectious Hepatitis," and Dr. Arthur R. Colwell, Sr., F.A.C.P., also of Chicago, discussed "Rationale of Good Control in the Treatment of Diabetes Mellitus." Dr. Cyril M. MacBryde, F.A.C.P., St. Louis, and Dr. Alfred Steiner (Associate), New York, also addressed the meeting, their respective subjects being "ACTH and Cortisone" and "Diet and Arteriosclerosis."

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Dr. Howard T. Karsner, F.A.C.P., Washington, D. C.; Dr. Roy W. Scott, F.A.C.P., Cleveland, and Dr. Robert W. Wilkins, F.A.C.P., Boston, were three of the participants in the Memorial Heart Symposium and Clinics, held in Winston-Salem, N. C., Sept. 25-26.

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Dr. Charles K. Friedberg, F.A.C.P., New York, delivered the annual Louis Gross Memorial Lecture on "The Current Status of the Treatment of Coronary Heart Disease" in Montreal, Can., on Oct. 16.

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Dr. Roger S. Mitchell, Jr., F.A.C.P., Trudeau, and Dr. Arthur J. Vorwald, F.A.C.P., Saranac Lake, were two of the speakers at the annual meeting of the Constantinian Society, which met at Saranac Lake and Lake Placid, N.Y., Oct. 1-4. Dr. Vorwald's address was on "Roentgenographic and Pathologic Manifestations of Various Pneumoconioses," and Dr. Mitchell's topic was "Recent Advances in Chemotherapy of Tuberculosis." The Society is composed entirely of internists who were chiefs or assistant chiefs of medicine in the Mediterranean Theater of Operations during World War II.

Dr. Louis F. Bishop, Jr., F.A.C.P., New York, was one of the out-of-state speakers at the recent annual meeting of the Rocky Mountain Chapter of the American College of Chest Physicians. His topic was "The Common Complications of Myocardial Infarction."

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Dr. Janet W. McArthur (Associate), Boston, led a round-table discussion on "The Adolescent Girl and Her Menstrual Problems" at the 21st Annual Meeting of the American Academy of Pediatrics when the Academy met in Chicago last month.

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"Psychoanalysis and the Biological Sciences" was the topic used by Dr. I. Arthur Mirsky, F.A.C.P., Pittsburgh, when he addressed a panel on research at the twentieth anniversary of the Institute for Psychoanalysis. The celebration was held at the Drake Hotel in Chicago on Oct. 11.

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Dr. Maxwell Finland, F.A.C.P., Boston, and Dr. Frank A. Evans, F.A.C.P., Pittsburgh, were the first two guest speakers at the Wayne (Mich.) County Medical Society's series of Monday night meetings. Their topics on Oct. 6 and Nov. 3 were, respectively, "Present Status of Antibiotic Therapy" and "The Subject of Obesity Comes up Again." Among the scheduled speakers still to be heard are: Dr. Henry W. Brosin, F.A.C.P., Pittsburgh, "Psychotherapy for the General Practitioner," Jan. 12, 1953; Dr. William S. Middleton, M.A.C.P., Madison, Wis., Beaumont Lecturer, Feb. 2, and Dr. Edward L. Bortz, F.A.C.P., Philadelphia, "Geriatrics," April 6.

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Dr. Hyman I. Goldstein (Associate), Camden, N. J., addressed the West End Clinical Society of New York on Oct. 9. His topic was "Errors of Priority Credit in Medicine's Forgotten Names."

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Col. Wayne G. Brandstadt (MC), USA, F.A.C.P., Editor-in-Chief of the *Armed Forces Medical Journal*, participated in the meeting last month of the Medical Editors of the World, and also attended the meetings of the International Congress of Medical Press, held in Venice, Italy, Oct. 4-5, and of the World Medical Association.

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Dr. Julius H. Comroe, Jr., F.A.C.P., Philadelphia, was one of the participants in the San Diego Cardiac Symposia, held Oct. 13. Later in the month, Dr. Comroe also lectured at the Los Angeles County Heart Symposia and at the 23rd Annual Postgraduate Symposium on Heart Disease of the San Francisco Heart Association.

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Under the presidency of Major General Harry G. Armstrong, F.A.C.P., the Surgeon General of the U. S. Air Force, the 59th Annual Meeting of the Military Surgeons of the United States is being held in Washington, D. C., Nov. 17-19. Dr. Howard A. Rusk, F.A.C.P., New York, is speaking on "The Utilization of Federal Professional Personnel;" and Dr. Louis H. Bauer, F.A.C.P., Hempstead, N. Y., is the principal speaker at the medical section panel.

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Dr. George H. Misko, F.A.C.P., Lincoln, speaking on "Problems in Allergy," and Dr. John R. Kleyla, F.A.C.P., Omaha, discussing "Management of Diabetes," were two of the speakers at the scientific meeting of the Nebraska Chapter of the American Academy of General Practice. The meeting was held in late September in North Platte.

Dr. Ray F. Farquharson, F.A.C.P., Toronto, Can., College Governor for Ontario, delivered an address on the "Diagnosis and Treatment of Jaundice" at the annual meeting of the Eighth District Branch of the Medical Society of the State of New York, when the group convened in Batavia, Oct. 16.

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Dr. Leon Lewis, F.A.C.P., Berkeley, Calif., has been recently appointed by the World Health Organization and the International Labor Organization to survey health conditions in factories in Iran. The survey is being made in response to a request from the Iranian government for help in putting into effect its new health legislation for the protection of workers. Dr. Lewis, formerly Head of the Division of Industrial Hygiene in the School of Public Health, University of California, Berkeley, will study working conditions in mines, handicraft shops, and carpet, match and tea factories, and will make recommendations to the Ministry of Health.

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After 26 years as a member of the faculty of the University of Colorado School of Medicine, Dr. James J. Waring, M.A.C.P., Denver, has been appointed Professor Emeritus. Relinquishing most of his teaching duties, Dr. Waring will nevertheless continue to be active in research and guidance at the Colorado Foundation for Research in Tuberculosis, of which he is Director and President of the Board of Trustees.

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Dr. Allen E. Hussar, F.A.C.P., has been transferred from the position as Chief of Medical Service of the Veterans Administration Hospital at Tuscaloosa, Ala., to the same position at the Veterans Administration Hospital, Montrose, N. Y.

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Dr. Ben E. Goodrich, F.A.C.P., participated in the Scientific Program of the 2nd International Congress on Chest Diseases at Rio de Janeiro, Brazil, August 27-30, 1952. "The Management of the Patient Dying of Bacterial Pneumonia" was the subject of his presentation.



## OBITUARIES

## DR. ARCHIBALD H. BEARD

Dr. Archibald Hildreth Beard, Sr., F.A.C.P., died in Minneapolis, Minnesota, on August 14, 1952, at the age of 62. At the peak of his career several years previously, he suffered from an attack of acute myocardial infarction. Upon recovery he retired from the practice of medicine and lived quietly with his family, though he maintained an interest in medical affairs and occasionally attended a meeting or a clinic at the University Hospitals.

Dr. Beard was born at Pueblo, Colorado, where he received his early education. He graduated from Kansas University, and obtained his medical degree from Harvard Medical School. He served under Dr. Richard Cabot at the Massachusetts General Hospital and then he came to Minneapolis where he engaged in the practice of medicine. During World War I he served in France with Base Hospital No. 26.

An accomplished and careful internist and a Fellow of the College since 1922, Dr. Beard was particularly interested in diabetes. As a member of the faculty of the University of Minnesota Medical School and a member of the staff of the University Hospitals, his wise counsel pertaining to the management of patients with diabetes mellitus was sought out by his students and his associates. Though burdened with a busy practice, Dr. Beard prized the opportunity to teach at the University Hospital. Following his retirement he was missed by his students and associates at the University, and now he is missed still more by his family and a wide circle of friends.

WESLEY W. SPINK, M.D., F.A.C.P.,  
Governor for Minnesota

## DR. N. BARNWELL HEYWARD

Dr. Nathaniel Barnwell Heyward (Associate) of Columbia, S. C., died suddenly while on his rounds at the South Carolina Baptist Hospital on June 3, 1952, of a coronary thrombosis. He had been in excellent health, active until the very end, and died as he would have wished, at his work.

Dr. Heyward was born December 27, 1886, in Columbia, S. C., and received his medical degree in 1911 from the Columbia University College of Physicians and Surgeons. After an internship at the Bellevue Hospital in New York, he returned to his home and was in active medical practice from that time until his death.

Dr. Heyward was an enthusiastic sportsman, an able practitioner of medicine and a loyal and tireless worker always in the interests of organized medicine. He served for two years as Secretary of the South Carolina Medical Association and declined reelection only a few weeks before his death. He was a past president of his county medical society, a member of the Southern Medical Association, and for twenty-five years served as the Executive Secretary of the South Carolina State Board of Medical Examiners. In this capacity, he combined boundless energy and enthusiasm with rare tact and unusual perspicacity for the work of selecting physicians for South Carolina. He had been an Associate of the College since 1927.

ROBERT WILSON, JR., M.D., F.A.C.P.,  
Governor for South Carolina

## DR. ABRAHAM KLEIN

Abraham Klein, M.D., F.A.C.P., was born in Brooklyn, New York, in 1883. He attended Polytechnic Preparatory School in Brooklyn, and started his medical education at Cornell University Medical College (1903-04). He received his degree in medicine from Long Island College Hospital in 1908. He then interned at St. Joseph

Hospital, Far Rockaway, Long Island. He went into the practice of medicine soon after. He was appointed Assistant in Medicine (1915-16), Associate in Medicine (1916-17), Attending Physician from 1918, Director of Medicine from 1937, and Consulting Physician, all in the Greenpoint Hospital, Brooklyn.

At the Jewish Hospital, Brooklyn, Dr. Klein served as Voluntary Assistant in Pathology (1910-12), and an Associate in Medicine in charge of the Department of Metabolism (1924-25).

He served in the Department of Welfare for eight years, and in World Wars I and II, he was an Advisory Medical Examiner for the draft boards.

He was most interested in metabolism and diabetes and had taken postgraduate work in New York and Strassburg, Germany. He was one of the earlier clinicians to take basal-metabolism recordings in Brooklyn, having worked with Dr. Du Bois.

Dr. Klein was a Diplomate of the American Board of Internal Medicine and had been elected to Fellowship in the American College of Physicians in 1925. He was a Fellow of the American Medical Association and a member of his state and local medical societies.

His patients and the members of the medical profession express deep sorrow upon his passing on April 27, 1952.

M. J. DATTELBAUM, M.D., F.A.C.P.

#### DR. ARTHUR JONES LOGIE

Dr. Arthur Jones Logie, F.A.C.P., died on June 13, 1952, of a pulmonary embolus resulting from thrombophlebitis.

Dr. Logie was born in New York City in 1907, and was graduated in medicine from the University of Edinburgh in 1933. He interned at the Edinburgh Royal Infirmary and served a residency at Sea View Hospital, New York City. Later, he became a member of the staff of Florida State Hospital at Chattahoochee, Florida.

During the years 1936 to 1941, he served as Director of the Tuberculosis Division of the Florida State Board of Health. Here, he was instrumental in organizing mass x-ray screening of the population for the detection of pulmonary tuberculosis. This effort proved remarkably successful, and has been continued on an increasing scale up to the present time.

Dr. Logie moved to Miami, Florida, in 1941 to engage in the private practice of medicine. For a while, he served with the U. S. Public Health Service in the Miami area.

Dr. Logie was certified by the American Board of Internal Medicine. He was a Director of the Miami Heart Institute, and Attending Physician at the Mercy, Victoria, St. Francis, Mount Sinai, and Jackson Memorial Hospitals. He was a member of the Dade County Medical Association, Florida and Miami Heart Societies, American Medical Association, American Trudeau Society, and the former Vice President of the Florida East Coast Medical Association. He became a Fellow of the American College of Physicians in 1940.

Dr. Logie was deeply respected by all who knew him, and his untimely death will be felt as a great loss by his many friends.

WILLIAM C. BLAKE, M.D., F.A.C.P.,  
Governor for Florida

#### DR. PAUL HENRY RINGER

Paul Henry Ringer, M.D., F.A.C.P., was, and will be, referred to as "Paul Ringer of Asheville," although he was born and educated in New York City and returned there in 1950 when he retired from the practice of medicine. His death occurred on May 8, 1952.

Dr. Ringer became a general practitioner in Asheville in 1906. In association with the late Dr. Charles L. Minor, F.A.C.P., and the late Dr. C. Hartwell Cocke, F.A.C.P., and several other physicians in Asheville, he promoted the modern views of the treatment of tuberculosis, made Asheville a recognized center for the treatment of this disease, and achieved national recognition.

Dr. Ringer was born November 6, 1881, in New York City, educated at Columbia, A.B., 1901, M.D., 1904; interned at St. Luke's Hospital, Bethlehem, Pennsylvania, and at Roosevelt Hospital, New York City. He was on the medical staff of the Mission Hospital from 1911 and the Biltmore Hospital from 1914, and he served in the First World War with assignment to the Italian Army. His activities in the community included work in the Civic Music Association, the Asheville Colored Hospital, the YMCA, the Good Samaritan Mission, the Civitan Club, and many others.

Dr. Ringer became a Fellow of the American College of Physicians in 1929, and, with Dr. Cocke, who was Governor and Chairman of the Board of Governors for many years, attended almost every meeting. He was Vice-President of the American Clinical and Climatological Association in 1932, President of the North Carolina State Medical Association in 1935, and President of the Southern Medical Association during 1940-41.

At the time he settled in Asheville, Dr. Ringer's friends and contemporaries must have thought that he was becoming a general practitioner in the backwoods. By giving unsparingly of his time and energy to his adopted community and his profession, he helped to make Asheville well known as a medical center and became a leader in his state and in the field of diseases of the chest.

ELBERT L. PERSONS, M.D., F.A.C.P.,  
Governor for North Carolina

#### DR. GRANVILLE NIMROD RYAN

One of Iowa's pioneer internists, Granville Nimrod Ryan, A.B., M.D., F.A.C.P., died July 18, 1952, at St. Joseph's Hospital, Pontiac, Mich., as the result of a cerebral hemorrhage. He was 82 years of age.

Born at Parmleysville, Ky., May 23, 1870, he came to Iowa with his parents at the age of ten. Following his graduation from Cornell College, Mt. Vernon, Iowa, he received his medical education at Rush Medical College in Chicago, being graduated in 1895. He served his internship in St. Elizabeth Hospital, Chicago, and then began more than half a century of practice in Des Moines, Iowa.

During his active professional career he attained prominence as a pioneer in both medical and civic life. He was the first President of the Medical Society of Missouri Valley, and also served as President of the Iowa Clinical Medical Society and of his county medical society. He was honored by the Iowa State Medical Society with the chairmanship of its board of trustees from 1910 to 1920. A Diplomate of the American Board of Internal Medicine, he became a Fellow of the American College of Physicians in 1920. He was a delegate of the Iowa State Medical Society to the International Congress of Medicine in London in 1913. From 1900 to 1914 he was a lecturer in the Drake University College of Medicine. He served his community as a member of the school board from 1918 to 1921.

He was married in 1903 to Miriam Pickens of Louisville, Ky., who survives him together with two children, Mrs. Moultrie Patten of New York, and Granville C. Ryan of Detroit. Following his retirement from active practice in 1948, Dr. and Mrs. Ryan moved to Detroit to make their home with their son. Dr. Ryan was buried at Colfax, Iowa, his boyhood home.

HERMAN J. SMITH, M.D., F.A.C.P.

## DR. THEODORE THADDEUS STONE

Dr. Theodore T. Stone, F.A.C.P., died on March 5, 1952, at his Singing Pine Farm near Woodstock, McHenry County, Illinois, after a long and painful illness.

Dr. Stone was born in Chicago, Illinois, on August 3, 1897, and received his B.S. degree from the University of Illinois in 1918, and his M.D. degree from the University's College of Medicine in 1920. Early in his career, he received the M.S. degree (1933) and Ph.D. degree (1935) in neurology from the Graduate School of Northwestern University.

He served as an interne in Cook County Hospital 1920-1922, and then resident in neurology and psychiatry 1921-1922 at the Cook County Psychopathic Hospital.

He joined the faculty of Northwestern University Medical School in 1922 with the rank of Clinical Assistant and continued in his advancement to the rank of Professor.

From 1922-1936 Dr. Stone was attending neurologist, Michael Reese Hospital; chairman and attending neurologist, Cook County Hospital (1936-1946); chairman of division and attending neuropsychiatrist, Wesley Memorial Hospital from 1942 until his death.

Dr. Stone held memberships in the American Academy of Neurology, American Association of Neuropathologists, American Board of Neurology and Psychiatry, American Medical Association, American Neurological Association, American Society of Industrial Medicine and Surgery, Association for Research in Nervous and Mental Diseases, Central Neuropsychiatric Association, Central States Society of Industrial Medicine and Surgery, Chicago Academy of Criminology, Chicago Medical Society, Chicago Neurological Society (former Secretary and President), Chicago Pathological Society, Illinois Psychiatric Society, Illinois State Medical Society, and the Institute of Medicine. He was a Diplomate of the American Board of Psychiatry and Neurology and became a Fellow of the American College of Physicians in 1949.

During World War II, Dr. Stone served his country as Neurological Consultant and Examiner for the Medical Advisory Board, Selective Service System.

Dr. Stone was a man of great energy and enthusiasm, an inspiring teacher, and able investigator. He worked well on a team and was an able leader.

He contributed about seventy papers to the neurological literature; and during the last two years of his life, when he was very ill, he published five papers. In addition, he was planning to present a paper at the Midwest Regional Meeting of the College in Chicago on November 22, 1952. What wonderful evidences of his great courage!

His family, colleagues, patients, friends, and students have lost a good neurologist, a good friend, a good companion, and a good man.

Dr. Stone is survived by his widow, Betty, four brothers and a sister.

HOWARD WAKEFIELD, M.D., F.A.C.P.,  
Governor for Northern Illinois

## COLONEL FRANK P. STROME

Colonel Frank Paul Strome (MC), USA (Retired), M.D., F.A.C.P., was born in Ashley, Pa., April 15, 1887, and died at his home in Drexel Hill, Pa., July 28, 1952.

Having received his M.D. degree in 1915 from the Medico-Chirurgical College, Philadelphia, Colonel Strome was appointed a First Lieutenant in the Medical Corps Reserve on June 20, 1917, and was promoted to Captain May 9, 1918. He was honorably discharged on September 13, 1920, to accept a commission in the Regular Army. Colonel Strome served at Walter Reed Army Hospital, the Army Medical

School, Gorgas Army Hospital, and at the Station Hospital, Fort George G. Meade, Maryland, prior to his retirement for physical disability in 1934.

He was recalled to active duty on August 24, 1940, and promoted to Lieutenant Colonel, March 26, 1942, and to Colonel, February 12, 1943. His principal duty during World War II from August 1, 1942, to January 13, 1946, was as Surgeon of the Third Service Command.

Between his tours of active duty, Colonel Strome was Director of the Bureau of Vital Statistics of the Commonwealth of Pennsylvania from 1935 to 1940; and from 1946 to 1948 he was Chief Medical Officer of the Valley Forge Military Academy, Wayne, Pa.

A member of the Philadelphia County Medical Society, the Medical Society of the State of Pennsylvania, and the American Medical Association, Colonel Strome had been a Fellow of the American College of Physicians since 1925.

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1. Cass, L. J., and Wolf, L. P.: *Gastroenterology* 80:149 (Jan.), 1952.

2. Berberian, D. A., Pauly, R. J., and Tainter, M. L.: *Gastroenterology* 80:143 (Jan.), 1952.



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\*Crosbain, G., Justice, T. T., and King, J. S., Jr., A New Approach to Increasing Tolerance to Oral Aminophylline—to be published.  
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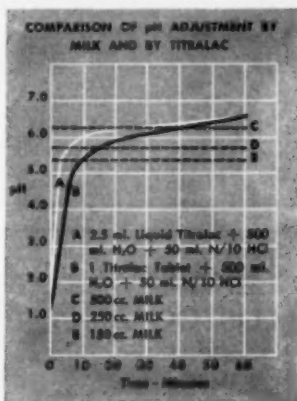
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1. Humphreys, P., et al: *Angiology* 3:1 (Feb.) 1952.
2. Plott, M.: *New York State J. Med.*, 52:2012-2014 (Aug. 15) 1952.
3. Perlman, A.: *Angiology* 3:16 (Feb.) 1952.
4. Samueli, S.S., et al: *Angiology* 3:30 (Feb.) 1952.

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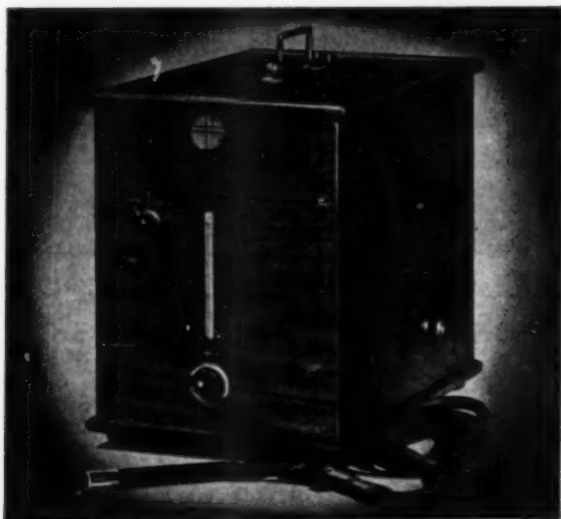
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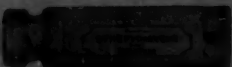
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